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Food and Drug Administration—Fiscal 1959 Report

The Effect of the Food-Additives Amendment on Food Processors and Others . . . . . .
FRANKLIN M. DEPEW

See Table of Contents for Articles in This Issue

A COMMERCE CLEARING HOUSE PUBLICATION

PUBLISHED IN ASSOCIATION WITH THE FOOD LAW INSTITUTE, INC.

The editorial policy of this JOURNAL is to record the progress of the law in the field of food, drugs and cosmetics, and to provide a constructive discussion of it, according to the highest professional standards. The FOOD DRUG COSMETIC LAW JOURNAL is the only forum for current discussion of such law and it renders an important public service, for it is an invaluable means (1) to create a better knowledge and understanding of food, drug and cosmetic law, (2) to promote its due operation and development and thus (3) to effectuate its great remedial purposes. In short: While this law receives normal legal, administrative and judicial consideration, there remains a basic need for its appropriate study as a fundamental law of the land; the JOURNAL is designed to satisfy that need. The editorial policy also is to allow frank discussion of food-drug-cosmetic issues. The views stated are those of the contributors and not necessarily those of the publishers. On this basis, contributions and comments are invited.

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REPORTS

TO THE READER

About the Authors

"The food, drug, and cosmetic industries and the Federal regulating agency, the Food and Drug Administration, are in the midst of changing times. It will require the unswerving efforts of all concerned to insure that the products controlled by the Food, Drug, and Cosmetic Act continue to be the best obtainable in this or other lands." So begins the fiscal 1959 report of the Food and Drug Administration, which is published in the recently released Annual Report of the United States Department of Health, Education, and Welfare, 1959, and which we are pleased to present to our readers in this issue of the JOURNAL.

"Steps forward in 1959," the report continues, "have included improved educational programs designed to combat medical and nutritional quackery, better industry sanitation programs, studies into the safety of food and drugs in this era of profound changes in composition and utilization, an effort to prevent debasement of supplies by those seeking illegal gains, and more industry and consumer educational activities.

"Management consultants were employed to seek an outside view as to whether facilities and procedures employed were effective, particularly in field operations. . . . The study clearly recognizes the magnitude of the enforcement task in these words:

" 'The administration of these laws involves effecting compliance with their provisions by a large number of establishments geographically dispersed throughout the United States. Over 100 000 industrial and related establishments, 56,000 drug and proprietary stores, 319,000 eating places, 373,000 retail stores, 2 million growers of fruits and vegetables, 6,000 wholesale fruit and produce dealers, 16,000 packing sheds, and approximately 330,000 commercial import lots, annually, are subject to one or more aspects of FDA's regulatory activities.

" 'A second characteristic of the job is its rapidly changing complexity. Advances in food technology—from growing to packaging and distribution, an increased number of new drug formulations and their applications, and the ever-widening application of nuclear energy to food products—pose a succession of new enforcement problems.' "

Following the FDA's 1959 report in the JOURNAL is a paper by **Franklin M. Depew,** who is president of The Food Law Institute. This paper, "The Effect of the Food-Additives Amendment on Food Processors and Others," was read before the Division of Food, Drug and Cosmetic Law, Section of Corporation, Banking and Business Law, American Bar Association, during the ABA's annual meeting in August.

Bernard L. Oser, president and director of Food and Drug Research Laboratories, Inc., participated in the Fifth International Congress on Nutrition, which was held in Washington, D. C., early in September. He discussed modern technology as related to the safety of foods, stressing modern

versus ancient food processing and outlining the functions of food additives. "Today science has not only given us many new and useful substances," writes Mr. Oser, "but has taught us to identify the chemical components of our foods. What is more significant, however, is the fact that we now use techniques and tools capable of revealing slight or subtle physiological changes induced by chronic or lifetime ingestion."

"Food Additives as Viewed by the Food and Drug Administration" was the paper delivered last August by **J. Kenneth Kirk** at a meeting of the American Veterinary Medical Association in Denver, Colorado. Mr. Kirk is an assistant to the Commissioner of the Food and Drug Administration. He began his Food and Drug career as a junior inspector in 1930 and did inspection work in New York, Buffalo, Pittsburgh and Philadelphia, where he served as chief inspector from 1937 to 1940. He then specialized in regulatory work on food in the Washington administrative office until 1956, when he was appointed chief of the Food and Drug Administration's Boston District. Mr. Kirk's contributions to the service were recognized in 1955 by a Certificate of Merit from the National Civil Service League and in 1956 by a Superior Service Award from the Department of Health, Education, and Welfare.

Meeting

Fifth International Congress on Nutrition.—Franklin M. Depew, president of The Food Law Institute, Inc., has prepared the following note on his attendance at the recent nutrition congress in Washington:

The Fifth International Congress on Nutrition was held in Washington, D. C., September 1-7, 1960. This important meeting was attended by a distinguished group of some 2,000 nutritional scientists and others from all over the world. During the course of the congress, a number of symposia and panel discussions were held covering all phases of the latest advances in nutritional knowledge. Dr. Charles Glen King, executive director of The Nutrition Foundation, was president of this congress. At the opening session the welcoming address in behalf of the United States Government was made by President Dwight D. Eisenhower. Among the distinguished persons attending the congress were Drs. Biney R. Sen of the FAO; R. C. Burgess and M. G. Candau, both of the WHO; Elmer V. McCollum of Johns Hopkins University; William J. Darby of Vanderbilt University and chairman of the Food Protection Committee of the National Research Council; Carlos A. Grau, chairman of the Drafting Commission of the Latin-American Food Code; W. H. Sebrell, Jr., Institute of Nutritional Sciences, Columbia University; and Abraham Horwitz of the Pan-American Sanitary Bureau of the Pan-American Health Organization.

Dr. Horwitz, speaking at the Symposium on World Food Needs and Food Resources, emphasized that the solution of many of the problems of nutrition required the adoption of sound food laws throughout the world. In the course of his address he made the following statements: "Much time may be saved if highly placed officials can be persuaded to become enthusiastic supporters of the nutrition education program. Their promulgation of laws and regulations governing food and nutrition practices can greatly accelerate the speed of the education process among the public at large."

WASHINGTON-

ACTION AND NEWS

In the Food and Drug Administration

September Report of Drug Seizures.—A total of ten drug seizures occurred during August, according to the Food and Drug Administration's September report on enforcement and compliance. They included chloramphenicol from an imported batch not certified in the FDA laboratories as required by law, with labeling which did not bear the warning statements required for this drug; secobarbital sodium capsules not meeting U. S. P. requirements for uniformity of capsule weight; tablets offered for restoring sexual potency in men and for other rejuvenating effects, and for the treatment of arthritis and rheumatism; an ointment offered for the treatment of hemorrhoids and piles; a lecithin and vitamin product offered for a wide variety of serious diseases, including arteriosclerosis and coronary thrombosis; and cod liver solubles offered for the treatment of aplastic anemia in chickens. In each of these latter actions it is alleged that the labeling is false and misleading because the article is not an adequate and effective treatment for the conditions for which it was offered.

Food Seizures.—Total food seizures for the month amounted to 47. A carload of wheat treated with a poisonous mercurial compound suitable only for use on seed wheat was seized en route to a flour mill. Two vitamin products were seized because they contained less than the declared amount of Vitamin B_1 and Vitamin B_{12}, respectively. Another vitamin preparation and a product purporting to supply supplemental dietary protein were seized because they did not bear the special dietary information required for intelligent use.

Approximately 290,000 pounds of food were seized on charges of decomposition, filth, preparation or storage under insanitary conditions, or being otherwise unfit for food. Prepared under insanitary factory conditions were whole wheat noodles, crabmeat and pickles. Held in storage under insanitary conditions were dried beans, peas, green coffee and mustard seed which became contaminated by rodents, and corn meal, rice, noodles and flour which became insect infested. Foods seized as economic cheats included a product labeled as "Pure Apple Cider Vinegar" which was actually a mixture of apple cider vinegar and distilled vinegar or acetic acid and water. Shipments of green beans and canned peas were found below the quality required by the federal standard. A shipment of butter was seized because it contained less than the 80 per cent butterfat required by law.

Device Seizures.—Among the six device seizures for the month were two makes of so-called "air purifier" devices, which were seized on charges that their labeling was false and misleading. Also seized—on a danger-to-health charge—was a "stretch to health" device, consisting of a head harness and accessories, intended for supporting the head while the rest of the body dangles.

Voluntary Actions by Industry.—The amount of food involved in actions taken voluntarily by the food, drug and cosmetic industries to prevent unfit products from reaching consumers exceeds by many times the amount of unfit merchandise removed from the market by federal seizure action. For example, during the month of August 107 voluntary destructions of unfit products which came to the attention of FDA inspectors (and undoubtedly this is only a fraction of the total) amounted to $2,706.158 in original value. Reported expenditures for 13 voluntary plant improvements, on industry's own initiative or as a result of the Food and Drug inspector's recommendations, amounted to $165,000 for the month, and again this is undoubtedly only a fraction of the total.

Some of the larger voluntary actions included destruction of 600 tons of lettuce (by plowing under a 40-acre field) which accidentally became contaminated with the insecticide endrin during airplane application to another crop; expenditure of $10,000 to prevent rodent and bird contamination of stored grains, following recommendations of FDA inspectors; destruction of 21,600 pounds of sweet brine solution for pickle manufacture, when it became contaminated before use; and expenditure of $6,615 for a machine to improve drug control by copying orders direct from master formulas (eliminating possibility of typing errors) and to employ a trained pharmacologist in the control group.

Labeling Requirements for Dihydrostreptomycin Drugs.—New labeling requirements to assure the safe use of dihydrostreptomycin drugs for human parenteral (subcutaneous, intramuscular, etc.) use were proposed by the Food and Drug Administration on September 28.

Under the new requirements, outside wrappers or containers and the immediate containers would have to bear the statement:

"Warning: For use only in patients who cannot tolerate streptomycin" (for dihydrostreptomycin sulfate and for dihydrostreptomycin sulfate solution), or "Warning: For use only in the treatment of patients who cannot tolerate full doses of streptomycin" (for mixtures of dihydrostreptomycin and streptomycin).

The warnings would also have to include information to the effect that:

(1) *For dihydrostreptomycin*

Because of its potentiality for causing delayed deafness, the drug should be administered only to patients having infections amenable to treatment with streptomycin or dihydrostreptomycin, but for whom streptomycin is contraindicated.

For mixtures of dihydrostreptomycin and streptomycin

Because of its potentiality for causing delayed deafness, the drug should be administered only to patients having tuberculosis amenable to treatment with one or both of the drugs, but who cannot tolerate full doses of streptomycin.

(2) *For all of these drugs:*

Severe auditory damage has been reported following a total parenteral dose of as little as two grams to five grams of dihydrostreptomycin. The auditory damage, which is usually permanent, may be delayed for a few weeks or up to several months.

The proposed new requirements have been made necessary by discovery that auditory impairment or total deafness can result from use of a much smaller amount of the drug or use for a much shorter period than was formerly believed necessary to produce the injury. Prior to this new knowledge, labeling for the drugs was required to bear the information that frequent auditory and caloric tests should be performed on all patients receiving the drug on a *long-term* basis.

Interested parties are invited to submit written comments on the proposal within 30 days of date of publication in the *Federal Register* (September 27, 1960.)

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Journal

Food and Drug Administration—Fiscal 1959 Report

This Fine Report by the Food and Drug Administration Is Part of the Annual Report of the United States Department of Health, Education, and Welfare for Fiscal 1959. Stepped-up Education and Information Activities Are Reflected Throughout the Report.

THE food, drug, and cosmetic industries and the Federal regulating agency, the Food and Drug Administration, are in the midst of changing times. It will require the unswerving efforts of all concerned to insure that the products controlled by the Food, Drug, and Cosmetic Act continue to be the best obtainable in this or other lands.

New substances are being added to foods to permit commercial production and distribution of products that contribute materially to higher standards of living. Ninety percent of the active drugs now used in prescriptions were not known two decades ago when the safety of new drugs was first protected by law. They have saved many lives and permitted treatment of diseases that formerly were debilitating. Many are so potent that new measures of controls must be exercised in their manufacture and directions for use. Regulation of cosmetics has brought an end to the disfiguring preparations of the past, but too little is known about some of the new ingredients now being used. Farmers are using feeds medicated with potent drugs, and pesticides which require meticulous care to preclude unsafe residues in meat, milk, and eggs and on harvested crops.

All such developments add to the complexity of protecting the consumer and guiding manufacturers to assure the safety of their products. It requires research by industry, academic, and Government scientists and constant vigilance to see to it that their recommendations are followed.

The Food and Drug Administration had a full opportunity to learn the views of the groups affected by its activities during three day-long meetings held by the Secretary of Health, Education, and Welfare with representatives of national industry, professional, and consumer organizations in December 1958.

All of these groups vigorously advocated the continued strengthening of the Food and Drug Administration to meet its responsibilities in line with the Citizens Advisory Committee recommendations of 1955. Representatives said they want a bigger, better paid research staff, more educational work, a new central headquarters building to be constructed promptly, food additives work to receive prompt attention, food standards work to be resumed on a full-time scale, and public warnings against nutritional quackery to be continued.

Other recommendations, not unanimously shared, called for various amendments to the law—to require proof of the safety of new cosmetic ingredients, to change the requirements for coal-tar certification from the present "harmless" criterion to safe tolerances for intended uses, and to require proof of efficacy for new-drug clearance. Consumer groups spoke against any weakening of food standards provisions, while some industry spokesmen called for more flexibility. Many called for more enforcement of net-weight provisions, for adoption of the Uniform State Food, Drug, and Cosmetic Act by States that have not done so, and for better support of State food and drug law enforcement.

These groups also presented their views before appropriation committees of Congress on continued strengthening of FDA. The appropriation bill enacted for the 1960 fiscal year will bring the rate of growth of FDA up to the minimum rate recommended by the Citizens Advisory Committee, which called for a 3- to 4-fold expansion within 5 to 10 years.

Seventy positions to staff the new Detroit District were added for 1959 to the slightly more than 1,200 on the total enforcement rolls at the end of the 1958 fiscal year. Sixty-one positions to start

the food additives work were added by a supplemental appropriation in 1959. The 1960 appropriation provided for 348 new positions, including 60 to augment the initial food additives staff.

A new district will be staffed at Dallas. At Atlanta where a new building is under construction similar to that at Detroit, the staff will be brought to full strength for the optimum use of expanded facilities. The increased appropriation will also provide for modern scientific equipment to bring 10 districts up to the Detroit equipment prototype.

The Detroit District, dedicated on May 14, 1959, is the first new district in 24 years, and occupies the only building ever built as an FDA laboratory facility capable of meeting the needs of changing times. The 18th district at Dallas will be its counterpart in design and facilities.

Research work will be advanced by adding 60 new people for the following specific projects:

To detect and identify pesticide residues
To determine effect of radioactivity on foods and drugs
To investigate presence of carcinogens in container waxes
To study presence of toxic properties in fatty acids
To investigate bacterial contamination of frozen foods
To develop methods of analysis for adrenal and cortex hormones
To provide additional effort in food standards and cosmetics

In addition, 15 new positions were established for food additives research.

Medical activities will be strengthened by 16 new staff members to work on the evaluation of new-drug applications, to study adverse effects of new drugs after they are in use, and to make clinical studies of quack drugs and devices. The increase will also provide 34 more jobs to strengthen compliance, regulatory and information activities, and administrative management.

While these developments provide a look ahead, rather than an accounting of stewardship for the year past, they indicate the areas in which consumer protection has been inadequate and in which better facilities were needed.

Steps forward in 1959 have included improved educational programs designed to combat medical and nutritional quackery, better

industry sanitation programs, studies into the safety of food and drugs in this era of profound changes in composition and utilization, an effort to prevent debasement of supplies by those seeking illegal gains, and more industry and consumer educational activities.

Management consultants were employed to seek an outside view as to whether facilities and procedures employed were effective, particularly in field operations. The management consultants recommended that the present system of district offices be continued as well as their administrative functions, which should be expanded to some extent. They also recommended more resident inspection posts. They suggested areas in which work plans and program management can be made more effective.

The study clearly recognizes the magnitude of the enforcement task in these words:

> The administration of these laws involves effecting compliance with their provisions by a large number of establishments geographically dispersed throughout the United States. Over 100,000 industrial and related establishments, 56,000 drug and proprietary stores, 319,000 eating places, 373,000 retail stores, 2 million growers of fruits and vegetables, 6,000 wholesale fruit and produce dealers, 16,000 packing sheds, and approximately 330,000 commercial import lots, annually, are subject to one or more aspects of FDA's regulatory actvities.
>
> A second characteristic of the job is its rapidly changing complexity. Advances in food technology—from growing to packaging and distribution, an increased number of new drug formulations and their applications, and the ever-widening application of nuclear energy to food products—pose a succession of new enforcement problems.
>
> Together these two characteristics have created a substantial gap between the job to be done and available resources—manpower, equipment, and facilities.

Training of new employees under the expansion program is a growing responsibility. Seventy-five percent of the inspection and clerical staff and 60 percent of the field chemists and Washington technical staffs have been with FDA less than 3 years. If the expansion provisions of 1960 continue, approximately one-third of the total personnel will be new in each of the next 2 years. A special training unit has been established to meet this situation.

Stepped-up education and information activities are reflected throughout the report. They have been designed to bring better compliance with the law by industry and better use of its protection by consumers. Industry and professional groups, consumer organizations, State food and drug agencies, and other Government departments with related responsibilities have contributed substantially to the growth of these activities.

Food, Drug, and Cosmetic Act—On the Food Front

Heavy rainstorms in many parts of the country caused flash floods which required supervised destructions of affected foods and drugs by local and State inspectors, with FDA help when needed. While individual losses from such storms were heavy in some cases, there were no disasters of the magnitude caused by floods and hurricanes in some previous years.

Potential Health Hazards.—*Deleterious Ingredients.*—Since 1957, about 4,000 samples of foodstuffs collected throughout the United States have been checked for radioactivity. The results disclose an increase in radioactivity of fresh vegetables above the "background" radioactivity normally present; evidence of continuing contamination in certain types of fish; an apparent increase in radioactivity in wheat collected in 1958 compared with that present in samples grown during the period 1945 to 1957; a continuing significant contamination of tea; and a wide range of radioactivity from fallout in samples of alfalfa hay and various ensilages harvested in 1958 and early 1959.

Only a limited number of samples have been analyzed to determine whether the radioactive material includes strontium 90. Alfalfa hay samples were found to contain up to 800 micromicrocuries [1] per kilogram of hay. Commenting upon this finding, Secretary Flemming emphasized that this radioactivity, by itself, is not a current threat to the public health. Strontium 90 has also been found in some samples of tea, but not in the samples of tuna which have been examined for it.

Samples of beans, peas, and fish from Peru have been analyzed for radioactivity during 1959. The results will serve as a guide for greater selectivity in import sampling.

Over 900 samples of bulk-tank milk were collected in 16 major cities of the country over a 4-month period to determine whether antibiotics, particularly penicillin, were used improperly in medication of cows, with residues in milk resulting. The penicillin residues were substantially reduced as a result of educational work following previous surveys and regulations providing for better label warnings and lower dosages. There are still present, however, small percentages of penicillin in market milk in some areas. FDA, working in close

[1] A curie is the amount of radiation given off by 1 gram of radium. A micromicrocurie is a millionth of a millionth of a curie.

cooperation with State and local health officials, will continue efforts to reduce the antibiotic residues.

Increased consumer protection from excessive pesticide residues on fruits and vegetables was provided by the planned collection and analysis of over 2,000 samples of crops from all commercially important growing areas and constant surveillance of the pesticide spray practices of growers.

These field investigations led to the finding of excessive DDT residues on a plant's entire pack of spinach being frozen for nationwide distribution. The crop had been sprayed with more than the recommended treatment 8 to 10 days closer to harvest than is directed to assure that unsafe amounts will not remain in the foods. After two large shipments were seized, the firm recalled the remainder of the pack throughout the country for destruction and inaugurated new controls.

The owner of a carload of lettuce, seized because of parathion and fluorine in excess of the tolerance, was an officer in two State associations of growers and shippers. Through these organizations he shared his object lesson with growers in a large area by warning them of the necessity of adhering to recommended schedules.

In another part of the country, inspectors encountered a crop of spinach that had gone to a packing plant the day after it was sprayed with parathion. When the canner was advised he destroyed 4,000 pounds of fresh spinach plus a small amount that had been processed. Additional truckloads of this spinach had been shipped to another food packer who had frozen it. At FDA's request, the firm held its stocks intact and after its own analysis disclosed excess parathion, voluntarily destroyed approximately 25,000 pounds in 10-ounce packages.

One district that had experienced serious spray residue problems the previous year sent out teams of inspectors and chemists, using trailer laboratory facilities, to devote more than 5 man-years to the program. In addition to inspections and analyses, discussions were held with grower association officers, commercial pesticide applicators, managements of chemical companies, and others concerned. During the entire year, only one high-residue lot was encountered in the territory covered by this district.

Spray residue problems are not, however, confined to growers who disregard the amounts and timing of applications. A residue of

DDE, a breakdown product of DDT, was found in carrots that had never been treated with DDT. Investigation disclosed that in previous years the field in which they were grown had been planted in cotton which had been heavily dusted with DDT.

FDA's concern that no pesticide residues endanger the milk supply led to the collection and analysis of over 300 samples of hay, silage, apple pomace, and field corn. Since most animal feeds of this type do not move in interstate commerce, samples which contained residues in excess of FDA tolerances were referred to State authorities to prevent use of such feed for dairy cattle. One State, for example, seized 248 tons of dried apple pomace with excessive DDT and warned all dairy operators and apple pomace producers of its potential danger to the milk supply. Federal seizure was made of hay with DDT, for which no tolerance had been established. This owner then warned the trade not to use pesticides that would make crops illegal. No excessive residues were found on feed crops sprayed with insecticides to control the grasshopper scourge in Colorado in the summer of 1958.

Twelve carloads of grain, aggregating 465 tons, were seized because of contamination with a mercurial compound. This is a known poison with legitimate use only as a seed treatment. Prosecutions were filed against three grain dealers distributing "throw-out" corn that had been so treated for seed use. Such corn, used by a manufacturer of poultry feeds, injured poultry and destroyed their egg-laying capability.

A leaflet "Protecting Crops and Consumers" addressed to farmers and agricultural leaders, and shippers of fresh fruits and vegetables was issued in December. It presents information intended to promote compliance with the pesticide chemicals law, with rules to be followed to make sure that pesticide residues do not exceed FDA tolerances.

A 16-State alarm was set off when the death of a child and illness of the rest of the family was traced to sodium nitrite in flounder fillets. Investigation disclosed that shipments of the contaminated lot had been confined to the area surrounding Haddon Heights, N. J., and that a number of other illnesses occurred. Outstanding portions were rounded up and the packing firm and its president and foreman were indicted by a Federal grand jury on charges that they had treated the fish with an injurious preservative with intent to mislead and defraud.

A sampling program began immediately after this tragedy to determine whether it was an isolated incident or whether other fish

on the market might also have been treated with sodium nitrite. The survey showed that nitrites are not generally present in fresh or frozen fish fillets produced in this country. Eight seizures were made, mainly of imported frozen fillets and smoked and brined fish.

Other seizures of contaminated foods included powdered eggs containing salmonella organisms, cheese with staphylococci, imitation vanilla with coumarin (a flavoring agent found a few years ago to produce injury to test animals), caviar containing a borax derivative as a preservative, and feeds containing mineral oil and fluorine.

Food Poisoning.—Forty-two outbreaks of suspected food poisoning involving approximately 1,200 persons were investigated by FDA during the year. *Staphylococcus* continued to be the most common causative agent and the majority of outbreaks developed as a result of insanitary handling or lack of adequate refrigeration.

Colby cheese prepared from unpasteurized milk was responsible for illness of more than 60 persons. Investigation revealed the cheese to be contaminated with large numbers of *Staphylococcus* and over 65,000 pounds were removed from the market by seizure.

In 14 outbreaks the specific micro-organisms or suspect food could not be determined.

To Keep Food Clean.—Sanitation programs have covered the entire food industry but have been concentrated largely on the procurement of suitable raw materials, since the processors as a whole are aware of their responsibilities to maintain adequate sanitation controls in their factories. Since producers of the raw supplies often are not interstate shippers, FDA has endeavored to persuade them to protect their products from filth and spoilage through educational programs conducted with the assistance of agricultural and industry groups, and by enforcement actions against interstate firms that will accept unfit raw materials.

Inspections were made of 3,218 food storage warehouses, including wholesale grocers, chainstore warehouses, cold-storage warehouses, and other establishments where food is stored for subsequent distribution. This represented a slight increase of time devoted to this project over that of 1958; it had doubled the previous year. Contaminated or insanitary lots were removed from human food channels by voluntary destruction or Federal seizure. A large number

of storage facilities were repaired and renovated to keep out pests and provide more sanitary storage.

Despite this progress some establishments were found on repeated inspections failing to protect stored products from contamination. Prosecution actions were filed against 18 firms during the year for holding foods under insanitary conditions. Among them was a wholesale flour distributor who was accepting return shipments from retail stores when the flour became contaminated with insects and rodent filth. This flour was sifted and packaged in new bags and distributed at a slightly lower price to lower grade stores. Seizures were made and the firm and its manager fined.

Table 1.—Actions on foods during the fiscal year 1959

Projects	Seizures	Criminal Prosecutions Instituted	Injunction Petitions
Total	828	111	13
Beverages and beverage materials	13	2	...
Bakery, ready to eat cereal, and macaroni products	13	12	...
Cereals and grain products:			
Human use	130	19	5
Animal use	4	7	...
Chocolates, sugars, and related products	18	12	1
Dairy products:			
Butter and churning cream	33	6	...
Cheese and other dairy products	6	2	...
Eggs and egg products	34	9	2
Flavors, spices, and condiments	25	1	...
Fruits and fruit products	58	3	1
Meat products and poultry	11	...	...
Nuts and nut products	103	2	...
Oils, fats, and oleomargarine	22	...	...
Seafood	73	12	1
Vegetables and vegetable products	106	5	1
Miscellaneous foods (mixed lots)	2	1	...
Warehoused foods	148	18	2
Food for special dietary uses*	27	...	...
Food adjuncts	2	...	...

* Includes vitamin products intended as food supplements.

Sampling of rail and truckloads of bulk wheat in the fiscal year 1959 resulted in 76 lots seized by Federal court action. Of these, 4 were seized for excessive damage by grain storage insects and 72 for contamination with rodent filth. Random samples taken during the course of the year indicated a distinct improvement in the sanitary quality of wheat since inauguration of the clean wheat program.

Concurrent with the sampling of wheat moving in interstate commerce, inspections are made of country elevators and terminal grain storage facilities in an effort to improve the sanitary practice of those firms. Through the cooperation of the Department of Agriculture, the Fish and Wildlife Service of the Department of the Interior, State colleges of agriculture, and county agents, the effort to improve grain storage is extended to the farm.

These educational efforts, together with injunctions and prosecutions, have resulted in destruction or abandonment of many old wooden elevators and repairs of others at large expenditures to put them in structural condition to protect grain from insects, rodents, and birds.

The magnitude of the wheat program is indicated by the fact that one injunction alone called for supervising the salvage of 150 carloads of wheat. Cooperating State food officials continued and materially expanded their own active programs. One State seized or embargoed 10 million pounds of wheat and other food grains.

In contrast to wheat, corn has many nonhuman food uses. This has presented difficulties in developing a program in the production of foods. An educational program has been initiated in the past year similar to the initial program in the "clean wheat" campaign. The Department of Agriculture and the Fish and Wildlife Service have joined FDA in issuing a leaflet "Clean Corn Will Pay Dividends," which was prepared in cooperation with the Corn Industries Research Foundation, Inc. Food industry and grain trade groups are assisting in distributing the leaflet so as to reach growers and handlers of food corn. Prevention of contamination not only means cleaner foods—it also means savings of millions of dollars through prevention of waste and destruction by insects, rodents, and birds.

The procurement of fresh, clean cream and keeping it so has for many years been the most serious problem of the butter industry, insofar as compliance with the Food, Drug, and Cosmetic Act is concerned. The major recent trend has been the churning of sweet cream only. An educational pamphlet issued by FDA in 1959 is entitled "Cream and Butter" (FDA Leaflet No. 9). It was prepared with the assistance of the American Butter Institute, as an aid to farm cream producers, cream station operators, and butter manufacturers. The industry, the Department of Agriculture, and State dairy officials have been assisting in its distribution to those responsible for the

sanitary handling of cream at all levels. It also discusses keeping the milk supply from being contaminated by drugs administered to cows.

The 1958 report discussed the problem of the diversion of incubator reject eggs into human food channels. Enforcement pressure and effective investigation of this racket came to a climax at a converted turkey-processing establishment near Newburgh, N. Y., in March. This "detective story" began with the closing of an illegal operation at Nashville, Tenn. This plant was moved and reestablished in Florida. In turn the Florida plant was discovered by FDA inspectors and, after a large seizure, it was surreptitiously dismantled, as was a breaking plant in Jersey City.

Equipment from both operations next turned up at the plant near Newburgh. Here a surprise inspection stampeded ringleaders who had operated in the other locations and they dispersed without putting into effect the warning system that had covered up their previous operations. This consisted of a buzzer alarm that warned employees to hide evidence of their illicit operations before inspectors were admitted. The employees were found continuing their regular operations—throwing the hatchery rejects into centrifuges and extracting everything liquid enough to come through. Then they froze the decomposed eggs in 30-pound cans. Federal seizure was made of 40,000 pounds, and State authorities supervised the destruction of the shell reject eggs not yet processed. A number of criminal cases have been filed and one operator has been charged with violation of a probation ordered in connection with a fine imposed for his Jersey City operations. See also "New Court Interpretations."

Filth or decomposition was charged in 79 percent of the food seizures; 7,430 tons were seized in 656 actions. Of these, 336 seizures involved merchandise that became unfit after interstate shipment. An additional 7,964 tons of unfit food were voluntarily destroyed or converted to nonfood uses by their owners as the result of FDA inspections.

These owners also reported 238 plant improvements costing approximately $4 million in the aggregate. Many have stated that the improved plant facilities and sanitary practices have more than paid for themselves through more efficient operations as well as in protecting foods from contamination and encouraging better employee concepts of sanitation.

Sixty-seven criminal cases charging shipment of filthy or decomposed foods were instituted. Sixty-eight prosecutions on like charges were terminated in the courts. Penalties ranged from probation to three jail sentences, of which one was suspended. The highest fine assessed was $4,500 against a warehouse and its president.

Twelve injunctions were requested to prevent the distribution of unfit foods. Five were against firms handling bulk grains, two involved incubator reject eggs, and one each confectionery, crabmeat, and canned tomatoes. Two were against warehouses. All were under injunction or temporary restraining order at the end of the year, except for one warehouse that corrected the insanitary conditions complained of; on its petition the court dismissed the case.

Pocketbook Protection.—With FDA's policy of giving top priority to problems of health and sanitation, and with a shortage of funds for enforcement activities in recent years, only limited attention was given to frauds and cheats. Increased manpower now permits more attention to protecting the consumer's pocketbook.

A nationwide check was made of the net weight of 36 different packaged foods—from soup to nuts—in cans, boxes, or bags. More than 111,000 individual retail packages from 100 wholesale lots of each food were weighed. Fifteen percent were short in weight by varying amounts. Nine percent of the lots examined were short by less than 1 percent, 3 percent were 1 to 1.99 percent short, 1.5 percent were 2 to 2.99 percent short, 1 percent were 3 to 4.99 percent short, and 0.5 percent were short by 5 percent or more.

A seizure program was initiated on significant shortages and attention to net contents practices of food packers will be a part of each food plant inspection in the 1960 fiscal year.

An intensified oyster inspection program in the Chesapeake Bay area for 11 days during the peak pre-Christmas packing season resulted in the filing of 11 criminal cases against packers observed to be soaking oysters longer than permitted by the FDA standard. Since excessive soaking is a practice that can be, and usually is, abandoned when an inspector enters the plant, lengthy or repeated inspections of 73 plants during this peak period brought many consumers better oysters for the holidays.

A 2-year Government-Industry Cooperative Oyster Research Project was launched in December. Its purpose is to acquire facts upon

which to evaluate the adequacy of the present standard and to suggest changes to strengthen consumer protection against excess water in oysters. The Fish and Wildlife Service of the Department of the Interior, the Oyster Institute of North America, and FDA are each contributing a scientist to the project.

More than a hundred seizures were made to protect the food buyers' pocketbooks. Included were watered orange juice, spent tea leaves and paprika, two brands of blueberry pancake mix with starchy purple pellets substituted for blueberries, coffee beans containing husks, black pepper containing buckwheat, and sirups and oils debased with cheaper ingredients. Among the items seized for failure to meet official standards were butter, cheese, oysters, shrimp, french dressing, salad dressing, and canned peaches, beans, mushrooms, and tomatoes.

Twelve of the oil seizures involved teaseed oil imported from Italy as olive oil. Fourteen other lots, totaling 89,000 gallons, were denied entry after FDA became aware of the situation. The two oils have practically identical chemical constants and special tests must be used to detect the adulteration. The teaseed oil was produced in China and reached Italy indirectly through the Iron Curtain for illegal manipulation and labeling. The Italian Government is reported to have taken action against the Italian firms involved.

Products of Special Dietary Significance.—To protect those for whom nutritional supplementation is required and those whose diets must be restricted in the management of certain diseases, the law requires special dietary items to conform to the labeled composition and to bear informative labeling to guide in their use.

Twenty-eight seizures were made of products failing to meet the vitamin potency claimed on the labels. Other violations were failure to set forth the minimum daily requirements of the vitamins declared on the labeling, and failure to list the sodium content of crackers and canned tomatoes offered as special dietetic items for persons on low-sodium diets.

Foods and nutritional supplements seized for false and misleading claims are discussed with misbranded drugs, since action was taken for violation of the drug provisions of the act. Many of them were offered for conditions that should be diagnosed and treated only by competent physicians.

Drugs and Devices

Recalls.—Twenty-seven defective or misbranded drugs were recalled by manufacturers during the year. Six antibiotics and seven other drugs were below labeled potency. One had decomposed in possession of dealers. Some bottles of an ear preparation were labeled for treatment of the eyes. Another label mixup involved the labeling of saline injection as dextrose. Four other injection drugs contained pyrogens or were nonsterile. Four contact lens wetting solutions were recalled from sale because they also were nonsterile.

One product was recalled because it had been distributed without a new-drug application, and two products being distributed under effective applications were recalled because of adverse reactions in some patients. The new drug applications were suspended in both cases, with the concurrence of the manufacturers.

An electrical device for treating mastitis in cows was recalled after seizures alleging that it was potentially dangerous to the treated animal and the person applying it.

Illegal Sales of Prescription Drugs.—Of 95 criminal actions charging drug violations, 72 cases involving 140 defendants were filed on charges of illegal sales of prescription drugs. Sixty-nine cases against 124 defendants were terminated in Federal courts in 1959 with 1 verdict of not guility for 3 individual defendants but guilty for the corporation. Jail sentences ranging from 6 months to 2 years were imposed on 8 individuals, in addition to 10 others that were suspended. Other penalties ranged from suspended nominal fines to $3,000 required to be paid.

State troopers have attributed many accidents to the use of amphetamine by drivers. The sale of such drugs is principally through truck stops, cafes, and drive-ins. It is definitely a bootleg type of business and is being pushed further underground in the hands of persons with criminal records for violation of other laws. Every effort is being made to trace the amphetamine tablets back to the point where they were diverted from legitimate drug channels.

Many States have been active in curbing illegal sales of this type and State boards of pharmacy have taken action against pharmacists convicted of violating State and Federal restrictions on the sale of prescription drugs.

Adulterated and Misbranded Drugs and Devices. — Litigation against the Hoxsey Cancer Clinic of Portage, Pa., was reviewed in some detail in the 1958 report. A contempt of court action, based on violation of the injunction, was filed in October 1958. To avoid punishment for this the "clinic" directors signed a supplemental consent decree of injunction which provided that they would close their establishment by November 1, 1958.

Two cases in 1959 were based on counterfeits of well-known brands of a tranquilizer. FDA cannot take the responsibility of protecting drug manufacturers' patent rights. It must, however, protect the public against drugs so formed that they may be palmed off for legitimate products which they do not meet in potency. The court assessed a substantial penalty, and two other individuals were under indictment at the close of the year. A manufacturer's private detective worked with FDA inspectors to get the evidence.

Two druggists were fined, given suspended jail sentences, and placed on probation for 3 years for substituting inexpensive cold tablets for an antibiotic prescribed for an upper respiratory infection. When the patient got worse instead of better, the physician became suspicious and referred the matter to FDA.

Cherry juice for arthritis, cabbage juice extract for ulcers, 62-cents-a-piece pollen candy for longevity, and royal jelly for sexual vitality are but a few examples of the 83 drug seizures charging false and misleading therapeutic claims. Conditions listed in the labeling ran the gamut from "that tired feeling" to diabetes, tuberculosis, and cancer. Promotion of royal jelly as a rejuvenator has continued despite seizures for the past 3 years. While medical research is being conducted into the relationship, if any, between certain heart ailments and the kind of fats consumed, food fad promoters are offering worthless products to protect against heart disease. Sufferers from arthritis and other conditions related to aging are the target of many quackery schemes.

The American Medical Association has estimated that overweight Americans are spending $100 million a year on spurious diet aids and useless mechanical devices. The 1958 annual report mentioned the joint efforts of the AMA, The National Better Business Bureau, and FDA in an educational campaign against nutritional quackery. These have been continued throughout the year, with the strong support of Secretary Flemming, whose warnings were published in newspapers

throughout the country. These same groups have extended this educational work to warnings against the fraudulent products and schemes being foisted upon the public as weight reducers.

Purported appetite depressants, food supplements, and other products are often offered with a plan including a low-calorie diet which alone produces the results, if any. Among the purported reducing agents seized were cigarettes and chewing gum.

Fifty-seven devices were seized for false and misleading claims. Many of them were electric vibrators offered for weight reduction. They included hand units, cushions, chairs, tables, mattresses, belts, and rollers. Some were also promoted for the cure of serious diseases. Vibration from these devices may provide temporary relief for minor aches and pains due to overexertion or fatigue, but they will not reduce weight or cure disease.

Other misbranded devices seized included chemical and radio diagnostic devices, do-it-yourself hypnotism records, therapeutic lamps and blankets, foot exercisers, vacuum cleaners, and time-honored copper charm bracelets, each falsely claiming to cure or prevent a long list of serious conditions for which they were worthless.

Apart from vitamins, covered under products of special dietary significance, 36 drugs were seized because they failed to meet official or declared composition. Also seized were 12 lots of condom prophylactics and clinical thermometers that were defective.

Four injunctions involving drugs and devices were requested of the courts during the year. One concerned adulterated injection drugs sold without an effective new-drug application. The other three were requested because of false and misleading therapeutic claims. They involved a cream and lotion, a so-called appetite depressant, and a pad containing pulverized rock falsely purported to contain uranium with healing properties.

Medicated Feeds.—The medication of a large proportion of prepared feeds to stimulate growth or treat disease in food animals has added materially to the regulatory obligations of FDA and State feed control officials.

Many of the new drugs used in medicated feeds produce profound physiological and pharmacological effects upon animals even when present in small amounts. Not only must the safety of foods derived from animals fed medicated feeds be established, but the in-

corporation of potent drugs in feeds at low levels requires exacting manufacturing and laboratory controls. Four shipments of feeds containing antibiotics were seized because they did not comply with certification requirements, or contained less of the drug than declared, or because another drug had been substituted for the antibiotic claimed.

New Drugs.—During the fiscal year, 448 new-drug applications including 79 for veterinary use were received; 273 including 43 veterinary applications became effective, permitting the products to be marketed. In addition, 1,067 supplemental applications including 377 for veterinary use were made effective. Two effective applications were suspended. No order was issued refusing to permit an application to become effective. One drug was exempted by regulation from prescription dispensing.

Included in the list of drugs allowed to be distributed under effective new-drug application were: Two oral antidiabetic agents; one antibiotic and one sulfonamide for the treatment of infections; eight drugs useful in psychotherapy; one narcotic and one mild analgesic agent for relief from pain; one antileukemic drug; a reserpinelike alkaloid for the treatment of hypertension; a drug which increases the excretion of uric acid in gout; a new steroid for the treatment of rheumatoid arthritis and other collagen diseases and a steroid with anti-inflammatory action for topical use only; a progesterone derivative for menstrual disturbances; two proteolytic enzymes for the cleansing of wounds and three antiseptics; a radioactive isotope for diagnostic use; three drugs to lower intraocular pressure in glaucoma; two vasodilators useful in vascular diseases; a skeletal muscle relaxant; one appetite depressant and two drugs for relief from vomiting; two antihistamines; a local anesthetic for dental use; two intravenous preparations, urea to decrease intracranial pressure and an amino acid to relieve a certain type of hepatic coma; and three diuretics for the treatment of congestive heart failure.

It is a part of the safety requirements for new-drug clearance that the applicant show that adequate manufacturing controls will be maintained. A number of seizures made during the year were of products manufactured by firms which did not have this clearance, although there were effective applications for the drugs themselves when manufactured by firms that had established adequate processing controls.

Among the drugs covered by the applications processed for veterinary use were: Two antibiotics for growth promoting effects; 2 tranquilizers for use in feed as growth promotants; 1 long-acting sulfonamide for treating systemic infections in farm animals; 10 corticosteroids with the trend to the more potent, somewhat specific agents such as Dexamethasone; 5 injectable iron preparations for treatment of baby pig anemia; and 3 anesthetics, 2 parasiticides, 2 diuretics, and 2 preparations for the treatment of dermatoses.

As a result of the food additives amendment, a number of veterinary new-drug applications and supplements to existing applications were refused on the basis that adequate information was not available to show that the product would not cause cancer.

Cosmetics and Colors

Three cosmetics were seized under the drug provisions of the act because they were falsely labeled, two for rejuvenation of the skin and one for curing dandruff. An eye lotion was voluntarily recalled by a cosmetic firm when its consulting laboratory reported bacteria and mold in several batches.

Certification Services

Coal-Tar Colors.—All coal-tar colors used in foods, drugs, and cosmetics (except hair dyes) must be from batches certified as harmless by FDA. In 1959, 5,262 batches representing 7,348,717 pounds were certified, and 22 batches, representing 23,774 pounds, rejected.

Insulin.—All batches of insulin must be tested and certified before distribution. Examination of 350 samples resulted in the certification of 288 batches of 7 insulin drugs and 60 batches of materials for use in making insulin-containing drugs.

Antibiotics.—The predistribution testing and certification of certain antibiotics is also provided by amendments to the act. Examinations were made of 13,716 batches of penicillin, chlortetracycline, bacitracin, chloramphenicol, dihydrostreptomycin, streptomycin, tetracycline, neomycin, nystatin, erythromycin, novobiocin, polymyxin, oleandomycin, and oxytetracycline during the fiscal year. The last seven antibiotics are not included in the certification amendments, but are tested when they are mixed with those requiring certification. Twenty-seven batches were rejected for failing to meet the following standards:

Potency (15), sterility (5), moisture (5), and pyrogens (2). In addition, manufacturers withdrew their requests for certification of 15 batches because they were substandard.

Enforcement of Other Acts

A total of 109,809,995 pounds of tea was examined under the Tea Importation Act. Rejections for failure to measure up to the standards set by the U. S. Board of Tea Experts totaled 99,367 pounds, or 0.09 percent. Three rejections were appealed to the U. S. Board of Tea Appeals, which upheld the decision of the FDA examiner in one case and sustained the appeal in one. The third was voluntarily withdrawn by the importer.

Three shipments of a bowl cleaner were seized for failure to bear the word "poison" as required by the Caustic Poison Act. A fourth seizure involved a grill and fryer cleaner containing more than 10 percent sodium hydroxide which was not labeled "poison" and did not give adequate directions for treatment in case of accidental injury.

No permits were issued for importations of milk from foreign countries, nor were any actions instituted under the Filled Milk Act.

New Court Interpretations

Four petitions for certiorari were filed with the Supreme Court during the fiscal year.

The Court accepted the Government's petition to review a Fifth Circuit Court of Appeals decision against the Secretary's order delisting for color certification FDC Orange No. 1, Orange No. 2, and Red No. 32. In reversing the Fifth Circuit Court, the Supreme Court agreed with the Department's construction of "harmless" and held that there is no authority under section 406(a) of the act to establish a tolerance for a poisonous coal-tar color.

The Supreme Court refused to review a Seventh Circuit Court of Appeals decision that a corporation cannot plead the fifth amendment as a defense for not answering interrogatories. The appeal included an attempt to establish that an agreement made with the Post Office would be "res administrata" and binding upon all other Government agencies.

In reversing a decision of the Court of Appeals for the Tenth Circuit upholding conviction of an individual for selling prescription drugs illegally, the Supreme Court remanded the case for a new trial

on the grounds that the jury may have been prejudiced by the newspaper publicity during the trial in the district court.

The 1958 annual report outlined litigation in a mineral water seizure that had been pending since 1953. The claimant asked the Supreme Court to review the entire case including the original decision of the Court of Appeals for the Eighth Circuit which reversed the jury verdict against the Government's charges that the labeling failed to comply with the dietary food regulations. The Supreme Court refused the petition.

Significant district court decisions included one holding for the Government in a case involving an insanitary wholesale grocery warehouse. The court observed that copies of analyses need not be furnished under section 704(d) of the act to warehousemen and that section 301(k) of the act is applicable to warehousemen who maintain insanitary establishments.

Findings of fact and conclusions of law handed down by a district court in a seizure case involving incubator reject shell eggs were significant because of the court's conclusion that shell incubator reject eggs are food within the meaning of the act regardless of the intended use of the eggs. This decision supports the statement of policy published in the Federal Register of September 5, 1958, holding incubator rejects to be adulterated if not denatured so as to preclude their use as food.

In another seizure case involving frozen whole eggs, the district court strongly supported the validity of bacteriological and chemical methods used by the Food and Drug Administration to establish decomposition in a product of this kind.

In a prosecution case involving a vitamin-mineral supplement, the district court, contrary to the decisions of numerous other courts, directed acquittal on his interpretation that the act does not apply to verbal misbranding.

Changes in Law and Regulations

The enactment of the food additives amendment (Public Law 85-929) on September 6, 1958, was discussed in the previous report. Its requirements went into effect March 5, with an additional year permitted to obtain clearance by regulation for substances already in use before January 1, 1958, and not generally recognized by experts as safe. (See "Regulations.")

Public Law 86-2, approved March 17, 1959, amends the act to permit the temporary listing and certification of Citrus Red No. 2 for coloring mature oranges under tolerances found safe by the Secretary. FDC Red No. 32, permitted by statute for coloring oranges, was dropped at the same time. The new color, developed especially for use on oranges, permits a greater margin of safety.

A number of bills that did not pass during the 85th Congress were reintroduced in the early days of the 86th Congress. Among them were bills to provide for the establishment of tolerances for colors used in foods, drugs, and cosmetics; the pretesting of new cosmetics; label warnings for hazardous chemicals; better controls over barbiturates and amphetamine; and a change in the labeling requirements for preservatives applied to crops after harvest. These bills are all pending.

Regulations

Drugs.—The labeling requirements of the insulin regulations were amended in March 1959 to require that after February 1, 1960, the expiration date must appear on each vial as well as on each package of an insulin-containing drug. Effective July 2, 1959, the term "insulin" was redefined to exempt from certification partially purified insulin intended for use in insulin-containing drugs.

Twenty-one new monographs and 417 amendments were added to the antibiotic regulations, and 423 permits were made effective to exempt medicated feeds from certification requirements.

A proposal was published, with opportunity for comment, on warning statements necessary for the protection of users of nonprescription drugs.

A statement of policy was issued on timed-release medicines, which have in some cases released potent medication too fast or at a slower rate than the physician expects. It provides that a multiple-dose product containing a quantity of active ingredient not recognized as safe for administration as a single dose must have an effective new-drug application, including data to establish that the active ingredients will be released as labeled.

Among the other policy statements published were a comprehensive statement on the labeling of drug preparations containing salicylates, a statement on the warnings required of nonprescription drugs

offered for use in minor sore throats, and a statement that injectable iron preparations for veterinary use are regarded as new drugs.

Food Additives.—Preprints of proposed food additive regulations were distributed on November 24, the first day of a well-attended 2-day food additive conference of FDA, members of the Food Law Institute, and representatives of the Manufacturing Chemists Association. These proposed regulations, published in the Federal Register of December 9, 1958, are both procedural and interpretive. They list 188 food additives proposed for exemption because they are generally recognized as safe for intended uses. The procedural regulations went into effect on March 28, but time was extended for comment on the proposed exemptions.

A second list of proposed exemptions, published on April 21, 1959, covers natural flavors and spices. Twenty-eight petitions for tolerances had been received by the end of the fiscal year and two were permitted on February 12, setting tolerances for an antioxidant to be used to protect forage crops from losing nutrients from oxidation, and establishing specified tolerances for this substance in meat and eggs of animals and poultry fed the treated feed.

The industry has been urged to avoid delay in filing applications for substances in use before January 1, 1958, and not generally recognized by experts as safe. A last-minute deluge of applications before the March 1960 deadline, or failure to file by then, would require discontinuing use of such substances, unless an extension of time is found by the Secretary to be justified and without danger to the public health.

Coal-Tar Colors.—Four dyes were removed from the list of colors certifiable for use in foods, drugs, and cosmetics because of tests showing them to injure test animals. Two have been used in butter, oleomargarine, and other oils and fats; the other two are little used in foods. These dyes are still permitted for use in externally applied drugs and cosmetics.

Because of injury to test animals, a proposal was made to remove 17 colors from the list of those certifiable for use in drugs and cosmetics, while continuing to certify 13 for use in externally applied drugs and cosmetics. Some of these colors are widely used in lipsticks, which are not considered "externally applied" because they are partially ingested and absorbed through the mucous membranes. The proposal has been opposed by drug and cosmetic manufacturers

who would be seriously affected by the delisting. Although there is no evidence that lipsticks now employing these colors are injurious, there is no authority under the act to establish tolerances for a coal-tar color found not "harmless" in any concentration.

At the request of the color manufacturing industry, specifications for a red coal-tar color for use in foods, drugs, and cosmetics were changed to improve the purity of this color.

A proposal was published to amend the regulations by providing for cancellation of certificates issued on colors subsequently delisted.

Pesticides.—In the fiscal year, 130 permanent residue tolerances or exemptions were established for the use of 22 pesticide chemicals on raw agricultural commodities. Since the enactment of the pesticide chemicals amendment, 2,070 tolerances or exemptions have been enacted for 104 pesticide chemicals. Six temporary tolerances were established for 1 chemical pesticide and 44 temporary exemptions for a microbial pesticide capable of killing insect pests but not injurious to man or other warm-blooded animals.

One of the tolerances established in 1959 permits the use of the antibiotic chlortetracycline in some forms of uncooked seafood to retard bacterial spoilage. The only other permitted use of antibiotics in food is for uncooked-poultry dips.

Food Standards.—Definitions and standards of identity were promulgated for six canned fruits to be artificially sweetened with nonnutritive substances. The words "artificially sweetened" are to appear on the label as the first two words in the name of each food. They are also required to comply with the labeling requirements of foods for special dietary use.

Standards became effective for frozen concentrate for lemonade, except for certain provisions that were stayed by objections requiring a hearing.

The identity standard for canned pears was amended to provide for the use, with label declaration, of artificial green coloring in mint-flavored pears and artificial red coloring in spice-flavored pears. An amendment to permit artificial red coloring in cinnamon-flavored apple and crabapple jelly was stayed by objections requesting hearings.

The standards for bakery products were amended to permit the use of limited proportions of wheat gluten to strengthen roll and bun dough, and also for loaves of raisin bread.

The sponsors of a standard for samsoe cheese petitioned to have the maximum moisture limit lowered from 46 to 41. This avoided a controversy with the manufacturers of swiss cheese, which has a 41-percent moisture limit.

Scientific Investigations

New problems of enforcement constantly arise and their solution requires continuous research along many scientific lines. The Bureau of Biological and Physical Sciences coordinates the work of seven scientific Divisions, each having its particular responsibilities. Their work is to develop methods of analysis; to evaluate the safety of pesticides and food additives; to work out effective specifications for certifiable antibiotic preparations, insulin, and coal-tar colors; to provide a sound scientific basis for administrative policies and to confer with representatives of the industries involved; and to improve certification enforcement and procedures.

During the past several years the divisions lagged in the application of the newer instrumental techniques to their scientific problems because funds for procuring the required equipment were not available. More recently, and especially during fiscal 1959, the situation has improved, and divisions are making increasing use of spectrophotometry, gas chromatography, X-ray techniques, electrophoresis, and spectrofluorometry.

Eighteen projects relating to improvements of methods for antibiotic assay have been completed, and 7 are in progress. An example is a microbial method which will detect as little as 0.05 unit of penicillin per milliliter of milk in 2½ hours. Twenty clinical studies on man, related to antibiotics (e.g., levels of antibiotics in blood and pain evaluation studies) have been completed, and one is in progress. In addition, 18 miscellaneous projects have been completed and 6 are still in progress. To illustrate, the fourth nationwide survey of fluid milk for antibiotic residues (1,170 samples) has been completed and the results have been published. In cooperation with manufacturers, over 300 batches of antibiotic diagnostic disks were checked for conformity with specifications.

Work continues on the determination of the exact chemical structure, the identification of intermediates, and the purity of certifiable coal-tar colors. Progress has been constant in the development of methods for cosmetic analysis in this field. A compendium of methods

of analysis for cosmetics has been composed, and will be ready for publication in the near future.

Development of methods for the detection and determination of pesticide residues, and analytical methods for detecting food additives, are important continuing projects. A corollary responsibility is the review of pesticide and food additive petitions.

Studies of decomposition in fish, eggs, and butter have continued. Progress has been made in the identification of the toxic principle which occurs in certain byproduct fats and causes a fatal edema disease in chickens. Various studies on milk have been completed and reported: The second nationwide survey of pesticide residues, the persistence of mineral oil residues as a result of mastitis treatments, the occurrence of heptachlor or its epoxide in milk as a result of feeding low levels of heptachlor to the cow, and the takeup of paraffin waxes by carton-packaged milk.

The bacteriological survey of frozen precooked foods has continued. Some 3,000 miscellaneous products have been examined, and a general report of the work to date is being compiled. It is expected to have a far-reaching effect on inspectional and bacteriological standards in the frozen food industry.

An improved procedure for isolating *Salmonella* from dried eggs has been developed. Significant progress has been made in devising a serological test for *Staphylococcus* and its enterotoxin. Both organisms frequently figure in food-poisoning episodes.

Work on methods of filth in foods continues. A revision of Food and Drug Circular No. 1, "The Microanalysis of Food and Drug Products," issued in 1944, was sent to the printer in June 1959.[2] Work also continues on the qualitative identification of drugs and their mixtures by means of a keyed classification of microcrystal identification tests.

In the past year much time has been spent in developing analytical techniques and checking new reference standards for a number of items which will appear in the 16th revision of the U. S. Pharmacopeia. The potassium bromide disk technique has been successfully applied to the infrared spectrophotometric determination of adrenal cortex hormones, barbiturates, ethinyltestosterone, quinidine, and several

[2] "Microscopic-Analytical Methods in Food and Drug Control," Food and Drug Technical Bulletin No. 1.

nitrate esters. A uniform simplified method for analyzing alkaloid-containing drugs has been developed.

A new chemical method for folic acid has been developed and published. A chemical method for vitamin D has been developed and, with some modification, has been adopted for inclusion in U. S. P. XVI.

FDA has been concerned over claims in labeling and advertising that enzymes have an established nutritional value. Experiments indicate that the normal animal has a tremendous capacity to produce the enzymes needed for the digestive process and that in the case of the normal individual there appears to be no need for supplementing the diet with enzymes. Studies of the effect of heat upon fats, and of the effect of food additives upon the nutritional status of the experimental animal are being continued.

Assay of desiccated thyroid by the U. S. P. chemical method for iodine content, and by bioassay for physiological activity, showed that desiccated thyroid stored at room temperature does not deteriorate over a 3-month period. Over long periods of time (20 years) there is a change in activity. Apparently there is no direct relationship between iodine content and biological activity.

Variability in the U. S. P. method for the assay of ACTH has led to a reexamination of bioassay procedures, and a new approach is being tested.

Work on the toxicity and metabolism of food colors continues. A study of aerosol hair-spray preparations showed that these products are not harmful when applied in the usual manner.

A 5-month clinical study of 1,100 surgical operations was conducted on postsurgical wound infections with bacteria cultures made of incisions at the time of wound closure, and if infection developed later all strains of *Staphylococci* were phage typed. Cultures were also made of nasal secretions of operating personnel to identify carriers of infection resistant to antibiotics being employed.

The pilot study on reporting adverse reactions to drugs continued as an active project. A handbook was completed on reporting procedures for use of participating hospitals. The ultimate goal of the study is a permanent reporting system.

Among the veterinary studies at FDA's Beltsville laboratory were a "pink eye" remedy, in a Freon-type container, for sheep and cattle. The tests showed that labeled directions were inadequate for proper

use and firms marketing similar items were informed that the distance recommended for spraying the preparation into the eyes of affected animals was so close that irritation resulted. Various injectable iron preparations recommended for use in the treatment of baby pig anemia are under study for efficacy and safety.

Enforcement Statistics

The 27,502 establishment inspections conducted by FDA were divided into 21,840 basic factory and warehouse inspections, and 1,813 of pesticide practices, 3,689 of public eating places to check on notification of the service of oleomargarine, and 160 involving illegal sales of prescription drugs. Of 29,747 domestic samples collected, 21,264 represented foods, 8,048 drugs and devices, 259 cosmetics and colors, and 176 miscellaneous.

In the 173 criminal actions terminated (or terminated for some defendants) in the Federal courts during 1939, fines assessed totaled $115,831. Jail sentences ranging from 1 month to 2 years were imposed in 22 cases involving 25 defendants. Twelve individuals were required to serve imposed sentences, averaging 8 months; they were suspended for 13, on condition that violative practices be discontinued. Records of actions terminated in the courts were published in 1,610 notices of judgment.

Table 2.—Number of samples on which criminal prosecutions and seizures were based and number of court actions instituted during the fiscal year 1959

Item	Total		Criminal Prosecutions Instituted		Seizures Accomplished		Injunctions Requested
	Violative Samples *	*Actions*	*Violative Samples*	*Actions*	*Violative Samples*	*Actions*	
Total	2,549	1,270	879	206	1,670	1,047	17
Foods	1,619	952	324	111	1,295	828	13
Drugs and devices	919	309	555	95	364	210	4
Cosmetics and colors	5	5	...	...	5	5	...
Caustic poisons	6	4	...	...	6	4	...

* The number of samples on which the actions are based always exceeds the number of actions; in seizures a variety of articles may be contained in a single shipment, while in criminal actions each sample usually represents a single shipment which forms one count of the acton.

Table 3.—Import samples collected, examinations made, and lots detained during the fiscal year 1959

Item	Samples Collected	Examinations Made	Lots Detained
Total	11,284	16,849	5,463
Foods	8,691	15,677	2,675
Drugs and devices	2,141	840	2,467
Cosmetics, colors, and miscellaneous	452	332	321

By FRANKLIN M. DEPEW
President, The Food Law Institute

The Effect of the Food-Additives Amendment on F

IN ORDER TO EVALUATE the tremendous impact of the food-additives amendment on the regulated industries as well as on the Food and Drug Administration, I sketch a brief history of the events leading to its enactment. This history shows the law to be part of a creative evolution whereby government and industry are continuously working together to better protect the public health.

Some years ago the Congress became concerned about the increased use of chemicals in the manufacture of food and the increased development of pesticide chemicals which might leave residues in food. The great technological advances since the war made available an infinite variety of new substances for preserving and improving food. The food industry had spent millions in improving the handling of raw materials and in food processes to produce cleaner and safer food. They had also spent millions in testing new substances used in food, but questions were raised as to whether these tests were adequate.

Investigations of these new substances were commenced by the House Delaney Committee, which held public hearings in 1950-1952. Subsequently the House Commerce Subcommittee on Health and Science held hearings during 1956-1958 and unanimously recommended that a law be passed requiring that food additives be pretested in a manner analogous to that required for new drugs.

This recommendation was made even though there was no evidence to show that any responsible food processor was using a harmful substance. There was a general conviction that despite this the public was in need of protection against small, irresponsible elements, as well as against the possible inadvertent mistakes of reputable food processors.

The recommendation for pretesting was supported by the food industry generally. The industry concluded that it was essential to

on Food Processors and Others

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resolve all doubts in favor of protecting the integrity of food products. Thus in deference to the national welfare, the members of the industry voluntarily recommended the relinquishment of some of their individual rights. By doing so they gave up the privilege that had been exercised by manufacturers through recorded history—the right solely to determine the safety of the food they manufactured in the manner it had been determined in the past, that is, by relying on the exercise of discretion and scientific judgment of their experts that it did not contain a poisonous or deleterious substance.

Prior to the enactment of the amendment, such a poisonous or deleterious substance might properly have been called a food additive within the meaning of the then-existing law. That law prohibited the food processor from using any poisonous or deleterious substance (that is, a food additive) except that if the substance was required in the production of a food or could not be avoided in good manufacturing practice, its quantity was not to exceed the limits of an administrative safety tolerance for it. During some 20 years no food additive was found to meet this exception in the law. As a result, where there was any question as to whether or not a new substance was poisonous or deleterious, the food processor usually reviewed his expert's conclusions with the Food and Drug Administration (FDA). Thus, these technological advances since the war had created a situation where the food processor, as a practical proposition, frequently felt he should not rely entirely on his own experts. Accordingly, with respect to such practices the amendment has but legally required the substantial equivalent of that which was theretofore done voluntarily.

I believe that most of the food processors will agree that up to the present time the amendment has not greatly changed their operations, so far as they relate to ingredients and processing substances, because it has only made mandatory what was previously done voluntarily. The situation, however, has been different with respect to packaging items. Food processors have had to explore more carefully the substances used in packaging materials, and thus they have brought to these suppliers a fuller realization of the law's requirements. I said "up to the present time" because the status of certain substances used in small amounts, such as many flavoring ingredients, is still unresolved. These substances are used in such small amounts they were not considered toxicologically significant in the past. The cost of testing each of these substances seems to be out of all proportion to the price at which the substance can be sold. The solution of the problem has been postponed by the granting of extensions for most of these substances until next year. It has been suggested that the amendment has presented the FDA and the industry with an insuperable problem in regard to these substances in that the requirements of the law may have outstripped our fundamental knowledge of toxicity. I do not believe that this will be the case. Much imagination and resourceful thinking may be necessary to solve the problem, but I feel confident a satisfactory solution will be reached.

As it has turned out, not only must the members of the food industry conform to the provisions of the amendment but the members of many other industries as well. It is doubtful that many of these other industries comprehended the manner in which the law would be applied to them. It is even doubtful that a portion of the food industry realized that the law would apply to those many substances present in foods in such small amounts they had been considered to be inconsequential from the standpoint of health hazard.

Necessity for Broad Definition of Term

The definition of the term "food additive" necessarily had to be broad in order to accomplish the desired purpose. It is so broad that it is now recognized that a company supplying processing materials, handling equipment or packaging material—in fact, almost anything —may be supplying a substance that constitutes a food additive. This is so because of the possibility that some portion of any substance coming in contact with food may migrate to the food. If that sub-

stance or any substance resulting from the interaction is not generally recognized as safe (GRAS), then both would constitute a food additive.

It seems obvious that it is mathematically possible for many millions of chemical reactions to occur almost daily as a result of the numerous contacts of various substances with food from the time the seed is planted until it reaches the consumer's table. In the past little consideration has been given to many of these possible reactions in the absence of any scientific warning that they constituted an imminent or even a potential danger to health. The new law has changed all this, for it poses a basic problem to the food processor and his suppliers —that of determining whether these multitudinous substances, many of which present serious practical difficulties of analysis, are generally recognized by qualified experts as safe for their intended use.

Responsibility for Solving Problem

The food and related industries have the primary responsibility of resolving this problem under the law. In order to answer the problem intelligently, it seems clear that all ingredients of all the processing and other materials must be disclosed to someone who is able properly to evaluate them and to determine whether the finished food does, or does not, contain or constitute an additive within the meaning of the law. At the outset this has presented the food processor with a vexing dilemma since the formulas for many of these items are regarded as industrial secrets of great value, which the proprietors are loath to reveal. So far as the exercise of this responsibility by the food processor is concerned, it is clearly essential that he be permitted a reasonable discretion in relying on the representations and guaranties made by his suppliers relative to the ingredients in the materials purchased, even though a guaranty may not fully excuse him from liability. Once he has collected this data, and has determined what all these materials are, it is still most difficult for him to find qualified experts who can evaluate the information.

It is most important to recognize, however, that the responsibility to solve this problem rests on management. In this connection it behooves the newly regulated industries, including the food industry, to reflect on the stern admonition of *U. S. v. Dotterweich*, 320 U. S. 277 (1943). This far-reaching decision, rendered only five years after the enactment of the Federal Food, Drug, and Cosmetic Act,

emphasizes that the remedial purposes of the Act require that it be liberally construed. The case involved a government prosecution against a drug jobber and its president and general manager. It charged that the corporation purchased certain drugs, repacked and labeled them in an adulterated and misbranded condition, and so shipped them in interstate commerce. The corporation was acquitted on technical grounds but the company officer was convicted. In the course of its opinion, the Court said:

> The prosecution to which Dotterweich was subjected is based on a now familiar type of legislation whereby penalties serve as effective means of regulation. Such legislation dispenses with the conventional requirement for criminal conduct—awareness of some wrongdoing. In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger. *United States v. Balint*, 258 U. S. 250. And so it is clear that shipments like those now in issue are "punished by the statute if the article is misbranded [or adulterated], and that the article may be misbranded [or adulterated] without any conscious fraud at all. It was natural enough to throw this risk on shippers with regard to the identity of their wares . . ." *United States v. Johnson*, 221 U. S. 488, 497-98.

These words of the Court warn of the extent to which management is held responsible for violations of the Federal Food, Drug, and Cosmetic Act. They merit most careful consideration at this time because of the new and difficult duties imposed on management by the food-additives amendment and the color-additive amendments.

The following further quotation from the *Dotterweich* decision gains increased significance in the light of these amendments:

> The purposes of this legislation thus touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection. Regard for these purposes should infuse construction of the legislation if it is to be treated as a working instrument of government and not merely as a collection of English words.

The *Dotterweich* decision is a precedent for the belief that the management of a corporation, as well as the corporation itself, which causes or allows a food additive to become a part of food are responsible for the adulteration of the food, even though they may have no personal knowledge of guilt. The law thus places great responsibility on management.

It has been said that even the most perfectly planned democratic institutions are no better than the people whose instruments they are. We see from the history of the food-additives amendment that it was framed in a democratic manner to further the public welfare. But the many unexpected problems created by its enactment leave some doubt

about the perfection of its legislative planning from the viewpoint of the many hazards involved in determining compliance. It is clear, however, that the language relative to "generally recognized as safe" expresses the philosophy that the amendment was not intended to make the law one of governmental permissive control. The success or failure of this new law will depend to a great extent on the measures taken to implement it by the officials responsible for its enforcement and by the management of the regulated industries. The FDA has responded admirably to the problems created by this enactment. Its regulations and interpretations demonstrate a helpful recognition of the difficulties which confront industry. Its "white lists" have been a major contribution in aiding industry to solve many of these problems. We believe this is what could be expected from this expert professional agency with its long record of distinguished administrative success.

Program of Education and Cooperation

However, the purpose of the amendment will not be achieved in time to come unless government and the regulated industries continue to use this same high degree of statesmanship in determining how compliance with its provisions can best be accomplished. We firmly believe that the regulator and the regulated have recognized that this is the case, and thus we conclude that the basic impact of the amendment has been to bring about a realization that it is necessary for all concerned to exert every effort toward making the amendment function in such a way that these multitudinous problems will be solved justly, fairly and effectively and with a minimum of conflict. We believe the law is largely and best self-enforced by industry on a voluntary basis and that every effort should be made to promote voluntary industry compliance through educational means before more drastic enforcement action is taken. The problems are so intricate and perplexing for scientists, as well as for lawyers, that they must be approached in a spirit of cooperation. If a dispute arises as to whether a substance is generally regarded as safe, it should only be carried to the courts with a sound appreciation by both sides of the issues involved. If the issue reaches the courts, it should then be determined impartially in accordance with our long-established history of fairness and justice. We believe we can look forward to the continued prudent exercise of responsibility and power which is so needed to make the law bring forth those ends which the Congress

intended. We have faith that the result will be in accord with the creative evolution which brought about the enactment.

In this connection it should not be forgotten that a major contribution in the past to the successful enforcement of the Federal Food, Drug, and Cosmetic Act has been the FDA's program of education and cooperation. The program has included the FDA's "open door policy," whereby voluntary industry compliance has been promoted by exchange of ideas about the interpretation of various provisions of the law. This program has been highly praised by all concerned with the problems of enforcement.

The FDA has deliberately adapted this tested policy to furthering compliance with the food-additives amendment. Not only has the FDA cooperated with The Food Law Institute in holding national FDA-FLI conferences on this subject but it has also expanded its "open door policy" to invite full and free discussion with its experts and other key personnel. These meetings have clearly demonstrated that a full explanation of all the facts relating to a problem, if presented in a spirit of cooperation, almost inevitably produce a satisfactory solution.

We of the FLI commend the FDA for this policy as the democratic way in which to develop respect for and compliance with any law. Such cooperation is in complete accord with the philosophy of our free institutions, and it should continue to have the full support of government and industry alike. One of the basic reasons why The Food Law Institute was created was to develop the needed knowledge about this and other aspects of the food and related laws by research studies, by university education and by other educational means. The FLI program of education will continue to be a bulwark of support for this method of law enforcement. We believe it is a privilege to participate in furthering this creative evolution by working together in this manner.

You were all saddened, I know, by the death of your beloved chairman and the first president of The Food Law Institute, Charles Wesley Dunn, who passed away just prior to the 1959 FDA-FLI Conference, which he worked so hard to make the success it was. He fought unceasingly to further the purposes of the FLI to the end that the laws we lawyers help make, expound and enforce might be fair and just.

We believe these purposes must be continuously fought for and cherished or they will be lost. The industry members of the FLI are

of this same opinion, and they are planning to expand our membership so that we may continue to develop our basic research and development program. They have greatly honored me by selecting me to administer this program as president of the FLI.

As part of this program we shall continue to cooperate not only with the FDA but with the food and drug officials of Canada, Europe, Latin America and elsewhere throughout the world. The trustees of the FLI acted with farsighted wisdom when they planned to familiarize the American food industry and their counsel with the progress of the proposed Latin-American and European Food Codes. I note in passing that I shall attend the Fifth International Congress on Nutrition, which will be held in Washington September 1-6. Dr. Carlos A. Grau of Argentina will report to this congress on the latest developments with respect to the Latin-American Food Code. The FLI intends to publish, in due course, an English translation of this latest official version of the code, so that you, as counsel, will have an opportunity to comment on its provisions to the end that this code shall eventually be adopted in the respective countries in a form which is sound and equitable. **[The End]**

FRANCE TO GRANT SPECIAL PATENTS FOR PHARMACEUTICALS

Pharmaceutical interests, long plagued by outmoded patent laws in many European countries, can now enjoy at least some relief in France, according to Allen R. Parker, director of the International Patent Bureau, Washington, D. C. French Law No. 59-250 of February 4, 1959 (effective June 1, 1960) provides for the issuance of "special patents" for the protection of new medicaments possessing curative or preventive properties with respect to human sickness and conditioned with a view to using them in medicinal doses. Patent protection can also be obtained on new products to be administered to human beings for medical diagnosis and new dietetical products which contain chemical or biological substances which do not constitute foodstuffs themselves but whose presence confers to such products either special properties of interest in therapy or properties of test meals.

Since this definition refers to human sicknesses only, products useful in veterinary medicine cannot be protected by special patents.

Any one special patent can protect only one medicament, that is, one chemical substance or pharmaceutical composition, so that the protection afforded by special patents is limited to one specific substance. Products of hygiene, if they do not contain poisonous substances, and products used for the disinfection of rooms and for artificial dentures are not considered as medicaments. Generally speaking, the French Patent Law of 1844, and its modifications, governing ordinary patents, applies also to these "special patents," with minor exceptions.

Modern Technology as Related to the

By BERNARD L. OSER

FACED WITH THE VAGARIES of climate and rainfall and the uncertainties of hunting and fishing, primitive man had to learn how to preserve his hard-won food. Thus it came about that methods of drying, salting and smoking were discovered. Yet these basic procedures, crude indeed by modern standards, are essentially the same as those employed in modern food processing.

Pickling, spicing and protection from air by covering with brine, sugar, sirup or fat, were among the more sophisticated processes developed by primeval and medieval man. Preservation by heating and deaeration, though known for many centuries, received its major impetus with the invention of the canning process by Nicholas Appert in France, and its development by him and his contemporaries, Thomas Saddington and Bryan Donkin in England.

Knowledge of the basic mechanisms involved in food preservation was largely empirical. Appert's method of hermetic sealing was predicated on the belief that putrefaction was caused by exposure to air. It was not until the significance of Louis Pasteur's germ theory was fully appreciated that a rational explanation could be advanced for the modus operandi of heat processing, as well as for many of the traditional forms of food preservation. It was Pasteur's contributions, perhaps more than any other single factor, that led to the development of food technology as we know it today. In the century that has elapsed since his discoveries, the effects of temperature, moisture, air and chemical milieu on the growth of microorganisms, and collaterally on enzyme action, have been exhaustively studied. This knowledge has not only provided explanations for the traditional means of food preservation, but has given rise to the variations, refinements, and improvements in technology introduced in recent times.

In view of current popular misconceptions propagated in certain quarters, to the effect that food processing, in devious ways, is directed

Safety of Foods

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toward making stale foods appear fresher, or inferior foods appear better, it may be profitable to consider how social and industrial progress have influenced food habits, and hence food technology. The development of world-wide navigation in the fifteenth and sixteenth centuries was stimulated in part, at least, by the search for easier routes to lands where spices were grown. But more than that, the long voyages on which ships embarked necessitated the preservation of the food supplies and of the foods brought back from the distant shores. Incidentally, it was not until hundreds of years later that it was realized that lemons contain a specific against sea-scurvy or that spices contain antioxidants and antimicrobial agents. When transportation by rail became the order of the day, migration occurred from farms and villages to towns and cities where the populations became increasingly dependent on foods raised and transported by others than the consumers. The distribution of food from farm to home has even to this day imposed special requirements on food processing by reason of (1) sanitary and health considerations of which we have become more cognizant since the advent of the science of bacteriology; (2) economic considerations related to the cost of shipping, storing and handling, down to the retail level; and (3) changing social customs and patterns of living, such as smaller living quarters, job-holding housewives, the vanishing tribe of cooks and servants, and the car for every home. The tremendous increase in food packaging, which developed from the foregoing considerations, and the concomitant legal requirements for labeling, which identified the manufacturer and promoted the use of the brand names, made it essential that food products meet, and consistently maintain, certain

standards of quality and uniformity. Suffice it to say, that in food production, processing and distribution, as in many other facets of life, *altera tempora altera mores.*

To revert to the main subject—the relation of technology to the safety of foods—let us consider the scope of modern processing techniques in contrast with basic, time-honored methods. Most of the operations used in food processing entail the application of one form or another of energy, chiefly thermal or mechanical—for example, the application of heat in such culinary operations as blanching, boiling, baking, broiling, roasting and frying, the major processing steps as they have always been. However, nowadays the objective is not merely preparative, but preservative, and the conditions are carefully controlled to effect sterilization, pasteurization or other desired objectives with a minimum of adverse change in nutritional or organoleptic quality. Modern food technology is, in fact, characterized throughout by the increasing use of quality control methods. Moreover, the conditions for heat processing are constantly being improved to permit optimum retention of flavor, texture and similar esthetic qualities, compatible with safety. Examples are the use of high-temperature, short-time processing and of aseptic filling in modern canning operations.

Many of the fermentation steps used from time immemorial in the production of bread, cheese, beer, wine, vinegar and various pickled products, are now rigidly controlled by means of known additions of enzymes, microbial cultures, and buffers, and the maintenance of uniform physical conditions. Moreover, many new enzyme products and special uses have been developed such as the *in situ* production of invert sugar in confectionery, the clarification of fruit beverages, the maintenance of whiteness in dried egg albumen and the decomposition of excess hydrogen peroxide used for bleaching purposes.

Among the most ancient food processing operations were the milling of cereals and the grinding of spices. These, together with fermented beverages, were incidentally the most easily, and hence the most frequently, adulterated foods. The development of analytical chemistry and microscopy during the last century marked the beginning of the end of such gross practices. This year we are celebrating the hundredth anniversary of the adoption of the English food laws. Today, milling is not merely grinding, but involves sifting, flotation,

and other types of physical separation, carefully designed to yield numerous products from wheat, corn, and other grains, with a variety of nutritional, organoleptic, functional and keeping properties. Some of these products entail the use of chemicals to restore or stabilize nutrients, to standardize leavening properties, or to improve the appearance and texture of the end product.

The aging of flour to facilitate the handling of dough in modern bread-making machinery and to maintain uniform loaf texture, is now accomplished by chemically controlled maturation. Many products derived from cereals and grains are subjected to mixing operations that involve extreme exposure to air, or to rolling, flaking, puffing, toasting, pressing and pelleting operations that involve elevation of temperature, either deliberately or incidental to the application of pressure. The effects of heat and aeration on the nutritional and safety aspects of foods must be considered in connection with the concentration, evaporation, and spray or roller drying of milk, fruit juices and other beverages.

Dehydration

Aside from canning, one of the most widely employed commercial processes for treating fruits and vegetables is dehydration. In place of the more primitive method of sun- or hot-air drying, this is now effected by exposure in trays or on moving belts under vacuum or in an inert gas, for example, nitrogen or the gases resulting from the controlled combustion of natural fuels. In order to prevent darkening of certain fruits, advantage is taken of the antioxidant effect of sulfur dioxide, ascorbic acid and erythorbic (isoascorbic) acid.

Certain processing operations are directed to the separation, isolation or concentration of various fractions of naturally occurring products. For example, peeling, sorting, screening, straining, filtration, deionization, centrifugation, extraction and distillation are aimed toward separating wanted from unwanted components of foods. To the extent that they involve the removal or leaching of vitamins or minerals, as may occur in the conveyance of fruits and vegetables through flumes or by flotation or washing, or the actual destruction of vitamins by excessive exposure to air, light or heat, these operations may influence the nutritive value of the final foods.

In the refining, deodorizing and hydrogenation of edible oils, high temperatures are employed. However, this is done under vacuum

or in an inert atmosphere (for example, in steam under reduced pressure) thus minimizing oxidative destruction. These operations may nevertheless affect the natural antioxidant content of vegetable oils and may cause heat-polymerization. The latter is also a factor of importance in the process of deep-fat frying of potatoes, fish, snack foods, etc.

Refrigeration

In this discussion of the manifold operations used in food processing, mention must be made of refrigeration, particularly in its more modern aspects involving subfreezing temperatures, the combination of freezing with drying or with antibiotics, and special conditions associated with packaging and distribution of frozen foods. These are not generally regarded as susceptible to nutritional deterioration or to changes of a hazardous nature. But when it is remembered that, except for precooked frozen foods, they are not usually subjected to preliminary heat sterilization, and that they are exposed to thawing either in the channels of commerce or prior to use in the home, the possibility of bacterial spoilage, even though slight, cannot be ignored.

One of the major innovations in the field of food preservation in our time has been the use, or rather the potential use, of ionizing radiations and high speed electron beams. This has been experimentally investigated most intensively from the standpoint of both functional practicability and potential hazard. Among the possible applications are the prevention of sprouting of potatoes, the destruction of insects in grains, cereals and spices, as well as the in-package sterilization of raw meat and fish. Whereas present indications show promise of limited usefulness of radiation as a pasteurization technique, either alone or in conjunction with other more conventional methods, serious limitations with respect to off-flavor development, particularly in meats, remain to be overcome in the case of complete sterilization. The higher radiation dosages required to inhibit enzymic, in contrast with microbial, deterioration may play a crucial role in determining the future of this means of preservation.

Lastly, but possibly of greatest current interest in relation to the safety of foods, are the large number of chemical substances whose numerous uses in food processing have only begun to be realized recently. (For the purpose of this discussion the term "food additive" will be used in its broadest aspect rather than as defined in the Federal

Food, Drug, and Cosmetic Act,[1] thus including any chemical substance present in food as a result of its use in production, processing or packaging technology.) On the one hand, a food additive may be present as an unintentional residue from the preharvest application of a pesticide to a plant, or from the administration of a drug to a meat- or milk-producing animal or it may be present incidentally from its use as a processing aid or from contact with processing equipment or packaging material. On the other hand, it may be intentionally added to impart a desired quality to the end product in which it is expected to remain. Regardless of whether or not it is purposefully present, the question of safety of an additive, in the amount present and under the conditions of intended use of the food, must be evaluated.

It is essential to stress the fact that we are not here concerned with the accidental contamination of foods nor with the deliberate adulteration of food, a practice so common in years gone by until it was largely curbed by food laws. The misuse of chemicals for deceptive purposes or through ignorance or carelessness is, of course, illegal and outside the scope of any definition of a food additive.

It follows that a food additive should serve a useful purpose directly or indirectly benefiting either the individual consumer or the public at large.

Functional Classes of Food Additives

From the functional standpoint, intentional food additives may be grouped into four major categories:

(1) Additives whose principal purpose is to enhance or restore nutritive value. These include vitamins, both natural and synthetic, mineral salts and certain amino acids.

(2) Additives in which the principal purpose is to maintain qualities of freshness or to protect against deterioration. These include (a) agents directed against chemically-induced or catalyzed changes, such as antioxidants, sequestrants and enzyme inhibitors; (b) agents directed against physically induced changes, such as emulsion stabilizers, anticaking agents, and humectants; (c) agents directed against microbially induced spoilage or hazard—inhibitors

[1] Federal Food, Drug, and Cosmetic Act of 1938, Sec. 201(s).

of bacteria, yeast or molds such as sulfites, benzoates, propionates, sorbates and antibiotics.

(3) Additives whose principal purpose is to improve or impart sensory qualities to food—flavor, aroma, color, texture or appearance. These include a large array of natural and synthetic flavoring, sweetening, coloring, thickening, bodying and gelling agents, waxes and other resinous glazes, and even carbon dioxide as used for carbonation. Many of the protective agents in (2) serve to maintain natural esthetic qualities of foods by preventing discoloration or off-flavor development.

(4) Additives whose principal purpose is to facilitate processing or handling, such as dough conditioners, lubricants (used in extruding, pelleting or other food handling machinery), antifoaming agents, solvents, emulsifiers, etc.

This classification of food additives is by no means complete and, of course, represents a considerable amount of overlapping in functional effect. No specific mention has been made of acids, alkalis and buffer salts, yet the regulation and stabilization of pH plays a vital role in many of these functions.

However, it should be apparent that the uses to which intentional food additives are put in modern technology do, in fact, result in real advantages to the consumer in terms of nutrition, sanitation, quality, convenience and economy—advantages which must be weighed against any possible hazards arising from their use.

Now let us consider some of the categories of so-called non-intentional or incidental food additives. These comprise substances used for some purpose in the raising or production of food which, despite good agricultural or technological practice, leave residues in the food:

(1) Pesticides, including insecticides, fungicides, rodenticides, acaricides, nematocides.

(2) Plant growth regulators including hormones, defoliants, herbicides, sprouting inhibitors.

(3) Animal growth promoters including certain antibiotics, organic arsenicals, estrogenic substances, and possibly enzyme preparations.

(4) Veterinary drugs including coccidiostats, antibiotics, tranquilizers, parasitocides.

(5) Processing equipment including kettles, trays, piping, valves, conveyor belts, etc. of metallic, rubber or plastic composition together

with the finishes, lubricants or detergents which may remain on their surfaces.

(6) Packaging materials including metals, plastics, paper, fabric, rubber or wood, and the lacquers, coatings, plasticizers, pigments and other components designed to impart certain physical properties adapted to the respective end uses of the containers or wrappers. Adhesives should also be included in this category.

There is no sound reason to believe that the proper use of pesticides and growth regulators impairs the nutritive value of food. On the contrary, by preventing rot, blight, and other plant diseases, by protecting against the depradations of insects, and by permitting harvesting under optimum conditions of yield and quality, agricultural chemicals contribute materially to the available food supply and to upgrading its nutritional quality and consumer acceptance. Prior proof of safety of residues of chemicals used for these purposes is, of course, required under the law. However, misuses are known to occur at times, resulting in the presence, for example, of DDT or penicillin in milk, or of aminotriazole in cranberries. Though such instances may constitute violation of legal tolerances, they should not be construed as seriously jeopardizing the health or safety of consumers, if for no other reason than that the levels actually found are generally well under maximum safe levels, and these, in turn, are based on large margins of safety applied to "no-effect" dosage to animals. Transgressions of tolerance limitations call for regulatory action but not for public alarm.

As was anticipated, the migration of additives from processing equipment, containers or other packaging material has posed many difficult problems under the new law designed to insure the safety of food additives. Of the large number of substances used in the fabrication of such products, many either do not migrate at all under normal conditions or, if so, in such small quantities as to present analytical difficulties which, in some cases, defy solution. Examples are the identification and determination of traces of petroleum hydrocarbons, or of low molecular weight polymers from wax paper and plastic film.

To meet this situation the Food and Drug Administration has indicated its intention either to waive the statutory requirement of a method for determining the amount of an additive in food, or to regard as "zero" any amount not detectable by a sufficiently sensitive analytical method.

That vigilance is required in respect to chemicals used under conditions where they may become unintentional additives to food is indicated by the recent discoveries that hyperkeratosis (X-disease) in cattle was due to a toxic lubricating oil used in a pelleting operation. Though it may not have involved hazard to human health, this episode revealed an unanticipated source of toxicity and justifies attention to the safety of all substances foreign to foods regardless of whether their presence is intentional or unintentional.

This condensed summary of the functions of food additives provides ample evidence of their technological justification, remembering always that no use of food additives is permissible which is deceptive or conceals inferiority. It remains to discuss whether food processing generally, and food additives particularly, affect the safety of foods —and if so, how this is established.

Safety of Food Additives

Since the enactment of the Food Additives Amendment, it has become apparent through orders of the Food and Drug Administration that hundreds of food additives are deemed safe by appropriately qualified experts judging either by experience in use, toxicological tests, or both. Many more have been considered safe and approved for use by the Food and Drug Administration or the Meat and Poultry Products Inspection Divisions of the Department of Agriculture. In addition, a large number of additives have been granted extensions for one year beyond the date when the amendment became fully effective, from which it may be inferred that the use of these substances involves no undue risk to public health. The final status of many additives will depend not so much on toxicity data as on evidence establishing whether or not they may become components of food in quantities sufficient to require consideration from the standpoint of safety or, if so, whether specifications for identity and purity are adequate to insure that the substances will be of satisfactory food grade.

It is not the purpose of this presentation to delve into presently unresolved questions concerning the safety of individual food additives. However, mention may be made of some of the broader problems that have beset toxicologists in industry and regulatory agencies. Several years ago inquiry was made into the matter of emulsifying and wetting agents to determine whether surface activity per se was a sign of potential toxicity. As a result a report was issued by the

Food Protection Committee in which it was concluded that there was no basis to support such a generalization and that each surface active substance would have to be evaluated independently.[2] Some nonionic emulsifiers, like the polyoxyethylene esters of fatty acids, actually lose their surfactant effectiveness upon hydrolysis in the gastrointestinal tract. Another question dealt with the possible harmful or irritant effect of laurates. A study of this problem by an *ad hoc* expert committee has lead to a recent report exonerating laurates as such.[3]

Undetermined or conflicting views regarding several other basic questions of toxicology might well be referred to expert committees for guidance in establishing general policy. For example, what level of nondigestible oil, such as mineral oil or hydrocarbon-like oils migrating from wax-coated or from plastic wrappers, can be safely tolerated? Or what are the toxicological properties of certain classes of organic compounds and to what extent are they influenced by characteristic groups, for example, mercaptans, allyl, vinyl and cyclohexyl compounds? Or, can safe levels of certain elements like cadmium, mercury, chromium, flourine, selenium or arsenic be established, bearing in mind that same have nutritional value and yet may be carcinogenic under certain conditions? Is it appropriate to regard oxalate deposition in the bladder, or any lesion which under exaggerated experimental conditions may ultimately develop tumors, as "precancerous" even when they are self-limiting or reversible upon removal of the toxic insult? Is synergism a sufficiently real, rather than theoretical, possibility at the level of concentration of food additives to demand consideration generally or only in special cases?

These are some of the vexatious problems that will have to be dealt with in the coming years as experience with the new law unfolds.

It is pertinent to recall the statement of the Joint FAO/WHO Expert Committee on Food Additives [4] to the effect that while it is impossible to establish absolute proof of the safety for use of any additive for all human beings under all conditions, critically designed animal tests can provide a reasonable basis for evaluating safety at a

[2] *The Relation of Surface Activity to the Safety of Surfactants in Foods* (Publication 463, National Academy of Sciences-National Research Council, October, 1956).

[3] Appendix, *The Safety of Glycerol Mono- and Dilaurates as Food Additives* (Publication 251, National Academy of Sciences-National Research Council, 1960).

[4] First Report of the Joint FAO/WHO Expert Committee on Food Additives, Rome, Italy, December, 1956.

specified level of intake which should be "substantially below any level which could be harmful to consumers."

According to the Food Protection Committee of our National Academy of Sciences-National Research Council, safety is the practical certainty that injury will not result from the use of a substance in a proposed quantity and manner.[5] The interpretative regulations under the Food Additives Amendment define safety more affirmatively to signify that "there is convincing evidence which establishes with reasonable certainty that no harm will result from the intended use of the food additive."[6]

Drawing Distinction Between Nutritional and Toxic Effects

Apparently then, the conditions of use are generally agreed to be all-important. But what about the nature or degree of harm that would constitute hazard? If a food process or a food additive should so damage a food as to render it unpalatable or inedible, does it follow that it is unsafe? Foods that are not eaten make no contribution to nutrition; on the other hand, unless they are eaten they are not unsafe. As a matter of fact, the proper use of additives to protect foods against deterioration in flavor, odor or appearance, render them safer than they would otherwise be. A change in concentration of a particular nutritional component as a result of processing does not justify the inference that harm will result from the ingestion of the food. If that were so, the milling of wheat to remove the bran and germ, or pasteurization of milk with concomitant loss of ascorbic acid, would be considered injurious. In evaluating the safety of a food, a distinction must therefore be drawn between any effect on its nutrient composition, which may occur before the food is consumed, and an injurious effect which may occur after the food is eaten, that is, as a result of local action in the gastrointestinal tract or systemic action following absorption. Excessive exposure to heat, light, air and water may reduce nutritional values. Traces of copper may reduce ascorbic acid content, sulfur dioxide may destroy thiamine, mineral oil may inhibit absorption of oil-soluble vitamins, but in none of these cases can we say that the effects are toxic. If the physical conditions of treatment or the use of chemicals

[5] *Principles and Procedures for Evaluating the Safety of Food Additives* (Publication 750, National Academy of Sciences-National Research Council, December, 1959).

[6] Federal Food, Drug, and Cosmetic Act, Sec. 121.1, Pt. 121—Food Additives Subpart A—Definitions and Procedural and Interpretative Regulations Under Section 409.

are such as to cause loss of nutrients in a food that is a significant source of the particular nutrients, it might be proper to regard them as unsuitable or unacceptable, but not on the ground that they are unsafe. This is not to say that the effects of processing on vitamin retention, on the digestibility and utilization of proteins and fats, and so forth, are not appropriate matters for evaluation by food scientists and for control by regulatory agencies, but the distinction between nutritional and toxic effects should be kept clearly in mind.

This suggests another problem that has arisen in experiments for the evaluation of safety. So strongly has the urge been to establish a no-effect level in animals at 100 times the human use level (as will be discussed later), that experimental rations have often been devised in which the test substance displaces a significant portion of the dietary essentials. It is not always possible for animals to compensate by eating excessive quantities of the diet mixture. Hence, the recommendation of the FAO/WHO Expert Committee that "dietary levels higher than ten per cent should not be used" ought to be consistently adhered to. In any case, safety appraisal should clearly differentiate between organic or functional effects induced directly by the test substance on the animal organism and those resulting from inadequate or irregular food intake or from changes in specific nutrients prior to ingestion.

The question may reasonably be raised at this point: "What have the procedures for safety evaluation to do with the impact of food technology on safety?" The answer depends, of course, on what we mean by safety. It may not be responsive, but it nevertheless is accurate to put the statement in reverse, that is to say that the time, cost and uncertainties of establishing safety have an increasingly important bearing on progress in food technology which the food additives law is designed to foster.

Selection of Dietary Feeding Levels

Decisions as to safety usually rest upon animal experiments which, even when well designed, entail more or less arbitrary conditions. The selection of dietary feeding levels is, of course, critical and several important facets of this phase of safety appraisal warrant discussion. For want of a more rational basis upon which to transpose safe levels for animals to safe levels for man "under the conditions of intended use," the safety factor 100 is generally employed with the blessing of

various official and quasi-official agencies. However, the factor is not always applied to the same parameters. Professor Frazer said in 1953:[7] "It has been agreed on a more or less arbitrary basis that food additives should be tested at various dosage levels *up to* 100 times the standard dietary dose." (Italics supplied.) He pointed out, however, that it was not clear how this should be applied. To quote further, "some authorities demand that no effects should result from the hundred-fold test dose, while others have not accepted substances that conform even to this rigorous criterion, and still others have suggested that substances should be rejected on the basis of invisible and undemonstrable changes that may have occurred. This last view denies the whole basis of observational and experimental science, and clearly makes any form of biological testing otiose." In view of the practical impossibility of establishing a no-effect dose with any degree of precision, Frazer proposed that if significant modification of structure or function could be observed in chronic feeding tests in less than half the animals at a 100-fold dose level and no effects were observed at ten-fold, the proposed dietary level could be regarded as acceptable. Nevertheless the FAO/WHO Expert Committee[8] (of which Professor Frazer was a member) stated that "where the maximum ineffective dose in animals is calculated in g/kg body weight a margin of safety of the order of 100 . . . is adequate" in the absence of any evidence to the contrary. This principle has been adopted by the United States Food and Drug Administration with the added explanation that "a food additive for use by man will not be granted a tolerance that will exceed 1/100 of the maximum amount demonstrated to be without harm to experimental animals."[9] To justify the 100-fold safety factor on the ground that man is ten times as sensitive as other species to certain drugs and poisons, and that individuals in various states of health and disease may vary ten-fold in sensitivity, is pure rationalization. Suitable comparative data on relative species sensitivity are meager at best and are predicated largely on acute or subacute toxicity. The relationship could be entirely different under conditions of chronic or lifetime dosage.

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[7] A. C. Frazer, 12 *Endeavor* 43 (1953).

[8] *Procedures for the Testing of Intentional Food Additives to Establish Their Safety for Use.* Second Report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization, Geneva, 1958.

[9] Federal Food, Drug, and Cosmetic Act, Sec. 121.6, Pt. 121—Food Additives, Subpart A—Definitions and Procedural and Interpretative Regulations Under Section 409.

At any rate the phraseology of the FDA regulation quoted above is ambiguous and confusing for several reasons:

(1) because it does not specify the units in which the "maximum amount" is expressed, that is, whether as ppm of test diet or mg per kg body weight of animal;

(2) because it does not make clear that the basis of expression should be the same under both the test and proposed use conditions;

(3) because in the legal sense a "tolerance" is the allowable level in a particular food, rather than in the diet as a whole, and is set not at the maximum safe level but at a level no higher than necessary to achieve the desired technical or other physical effect; and

(4) because it fails to specify that calculation of the human dietary levels should be on a dry weight basis similar to that employed in the preparation of test diets. Failure to take these factors into account could result in many-fold exaggeration of the assumed 100-fold safety factor for several reasons, namely, laboratory animals consume several times as much food as man in terms of dry weight (or calories) per unit of body weight; foods in which tolerances are established generally constitute only a fraction of the total dietary intake; and human diets are composed of foods that collectively consist of approximately two-thirds water.

In estimating probable levels of human intake, it has become customary to regard the maximum ingestion level of a particular food or class of foods as typical of actual daily intake. Moreover, the assumption is made that such ingestion is continuous throughout a lifetime. These exaggerations, in effect, further multiply the real magnitude of any assumed safety factor applied to dosages. It would seem logical, therefore, in interpreting the results of animal studies that more consideration be given to "patterns of consumption" especially as related to foods consumed only occasionally, seasonally, or for limited periods during the age cycle. Perhaps dietary levels should be estimated on a weekly, monthly or annual basis, rather than daily, and test feeding conditions adjusted accordingly.

Sensitivity of Analytical Procedures

The concept of zero tolerances for certain additives, especially those found (or suspected) to induce cancer in animals, raises questions of the sensitivity of analytical procedures and what will happen

when future methods will be devised of greater sensitivity than those currently in use. The principle should be recognized that at some finite minimal dose any substance can be administered with reasonable certainty that no harm will result.

Hence, insistence on "absolute zero" can only lead to absurdity. For instance, a food ingredient containing a pesticide residue within a permitted tolerance might be said to adulterate foods in which standards of identity do not provide for such residues; pure chemicals containing traces of arsenic or "heavy metals" within acceptable tolerance limits might be said to adulterate foods if any of these trace elements should be barred as carcinogenic to animals.

Consequences of Rigid Enforcement of Philosophy Expressed in Delaney Clause

The consequences of a rigid, nondiscriminatory enforcement of the philosophy expressed in the Delaney Clause are not too difficult to imagine. The observation in feeding trials that a chemical component—naturally present in spices or essential oils—induced cancer could eliminate that substance from foods regardless of whether it was present in its natural state or produced synthetically. It has been shown that roasted coffee [10] and smoked meat and fish [11] contain demonstrable amounts of benzpyrene and possibly other carcinogens. The finger of suspicion has been pointed to polymerized or epoxidized fats. Green leafy vegetables, alfalfa and other grasses as well as several other common foods have been found to contain measurable quantities of estrogens, another class of potential carcinogens. Compounds containing the allyl group have been found to vary considerably in toxicity, some being hepatotoxic or even tumorigenic upon chronic ingestion; nevertheless, this class of compounds is responsible for the characteristic taste of onions, mustard, radish and a host of other common vegetables and seasonings.

If experience cannot be relied upon to indicate that the ancient and honorable practices of preservation by smoking, frying in deep fat and seasoning with common spices are safe within the meaning of the Delaney Clause, our food habits will have to undergo radical change. On the other hand, if the rule of reason prevails and it is recognized

[10] M. Kuratsune and W. C. Hueper, 20 *Journal of The National Cancer Institute* 37 (1958).

[11] M. Dobés, K. Hopp and J. Sula, 1 *Ceskoslov. Onkol.* 254 (1955).

that there are safe levels even of dietary carcinogens, revocation of the absolute legal prohibition will follow.

It would be helpful if standards could be adopted to assess the weight of evidence advanced in support of causal relationships between dosage and response. For example, one might classify such relationships as ranging from negative to positive through intermediate steps, for example, (1) negative—unequivocal or proven beyond reasonable doubt; (2) hypothetical—based on an assumption without proof, that is, a tentative theory to explain certain effects and to serve as a guide for further investigation; (3) suggestive—based on indirect or qualified evidence, accepted with reservation subject to further investigation or consideration; (4) presumptive—based on sufficient evidence to justify a reasonable inference of a fact but not definitely proven; (5) positive—unequivocal or proven beyond reasonable doubt. These gradations of interpretation might be considered in establishing whether or not a substance is "found" to induce cancer in man or animals. Only presumptive or positive evidence should be considered as sufficient ground for denial of a tolerance.

Emphasis has been placed thus far on the interpretive, rather than procedural, aspects of safety evaluation because it is in this area that generally acceptable principles have yet to be established. Some eminent toxicologists have directed criticism toward the frequent insistence on chronic feeding studies as a *sine qua non* in the assessment of safety. Shorter and more economical procedures employing biochemical, metabolic or radiotracer techniques have provided sufficient information in some instances, but these have been relatively few compared to long-term studies. Where the substances under test are closely related to common components of foods, as, for example, mono- and diglycerides, sorbic acid, simple fatty acid esters, etc., short-term feeding tests or metabolic studies may be adequate.

Toxicological feeding studies must be planned and executed with due regard for possible metabolic pathways and for biochemical, pharmacological and morphological effects. In the investigation of sequesterants, for example, attention must be directed toward all phases of trace metal absorption and utilization, particularly hematopoiesis and systems involving metalloenzymes; studies of neurotoxic insecticides require consideration of cholinesterase activity; surface active substances may influence intestinal absorption and, if absorbed intact, the permeability of various cell membranes; compounds structurally re-

lated to vitamins or hormones may have antimetabolite effects; and so on.

The use of tissue culture preparations or of specific cell suspensions shows considerable promise of yielding fundamental toxicological data but either, like functional tests of target organs, must be interpreted with caution in relation to potential chronic effects in intact animals. The same may be said of single metabolic systems like the rate of glucose utilization, or of neurophysiological reactions like the conditioned reflex, as indicia of toxicity. Useful as they may be for purposes of revealing mechanisms of action, it is impossible to forecast when, if ever, these procedures will supplant long-range feeding trials in different species of animals as criteria for safety evaluation of food additives.

Conclusion

We have entered upon a new era comparable to that following Pasteur's foundation of the science of bacteriology which has had such a profound effect on the course of food technology. No single discovery, but rather the general growth of chemical science and industry in our own time, has had an impact on food production and processing as on every other aspect of our daily lives. The price of enjoying benefits will be careful attention to potential risks.

Fundamentally, the problems of safety are not new. In olden days they were attacked by the method of trial and error and the criteria were simply manifest injury or death. Food patterns were established by the process of elimination. Today science has not only given us many new and useful substances but has taught us to identify the chemical components of our foods. What is more significant, however, is the fact that we now use techniques and tools capable of revealing slight or subtle physiological changes induced by chronic or lifetime ingestion.

The application of these advanced methods and of higher standards of safety evaluation, proceeding concurrently with progress in agriculture, nutrition and food technology, has added a new dimension to the wholesomeness of our food supply. It is to be hoped that as new legislative and regulatory controls become adapted to changing conditions, balanced judgment will prevail so that technological progress can be assured at no sacrifice to the quality, variety and safety of our food. **[The End]**

FOOD ADDITIVES as Viewed by the Food and Drug Administration

By J. KENNETH KIRK

Mr. Kirk Is Assistant to the Commissioner of Food and Drugs.
This Paper Was Delivered August 16, 1960, at the American Veterinary Medical Association Meeting, Denver, Colorado.

THE FOOD-ADDITIVES AMENDMENT to the Federal Food, Drug, and Cosmetic Act was enacted in September, 1958, to become fully effective on March 6, 1960. The amendment, however, contained a provision authorizing extension of its effective date for up to one year where it could be shown that the extension was needed and would present no undue hazard to public health during that additional period. There is no provision in the law for further extension by administrative action.

This amendment is designed to give real consumer protection in a field in which it has long been needed. As the 1938 law read, there was no requirement that a firm preparing a food product contact the FDA prior to marketing that food. It was admonished to comply with certain sections prohibiting the use of unsafe components, and there was provision whereby legal action could be instituted if it were found that any added ingredient was poisonous or deleterious unless covered by a tolerance. The difficulty, of course, arose out of the fact that when a product was put on the market without adequate pretesting, the FDA had to find out about it, get samples, arrange for long-term toxicity studies in a laboratory which could not accommodate very many samples at one time, and then take legal action if the product were found to contain a poisonous or deleterious component. During all this time, which might be a period of years, the public would have been eating this particular food.

Even though the 1938 law did not require it, many manufacturers discussed with our pharmacologists proposals to incorporate various ingredients into their food, arranged for such toxicity studies as were

needed and did not market food containing the new ingredient until they and the FDA pharmacologists agreed on the question of the safety of the additive. Essentially what the food-additives amendment now requires is that each new substance be tested before the food is placed on the market and that in the case of foods already on the market, and not generally recognized as safe, a showing of safety be obtained before the products may be continued to be sold as food items after the effective date of the amendment.

The amendment defines a food additive as any substance which may reasonably be expected to become a component of food or otherwise affect its characteristics, whether added directly or indirectly; but it does contain certain exemptions.

The first of these exemptions involves those substances which are generally recognized as safe by experts qualified to evaluate them. This, of course, covers a great many substances. While the law does not so require, we have published several lists of food ingredients which we believe to be in that category. We already have many candidates for additional lists to be published in the future. There has been a great deal of misunderstanding as to what is meant by "generally recognized as safe"—GRAS, as this has become to be known. If a manufacturer has data showing safety and the FDA agrees that the substance is safe, but scientists generally do *not* know anything about that substance, it *cannot* be GRAS. In that situation the substance is a food additive and calls for a regulation to authorize its use.

The second exemption involves products for uses which have prior sanctions by the FDA and the Department of Agriculture Meat Inspection and Poultry Inspection Divisions. These fundamentally represent the items which were cleared with us prior to the enactment of the food-additives amendment even though the law did not at that time so require. In a sense, therefore, those who obtained clearance in those days are now reaping a sort of extra dividend. Incidentally, a prior sanction granted to one firm for a specific product for specific usage applies equally to all.

We have been importuned to publish lists of prior sanctions, but so far, with the exception of a few items in the packaging field, we have not found it possible to do so. It must be kept in mind that these sanctions were not given with the thought that they would be the subject of exemptions in a 1958 law and, thus, were not recorded in all cases so as to be readily located without extensive search of the files.

Then, too, some of the sanctions involved formulations which could be classed as trade secrets entitled to protection. If, however, anyone believes that a prior sanction of a specific item has been granted and if he will advise us of the name of the firm believed to have received that sanction, we will be glad to check our records to determine just what the situation is.

The third exemption, dealing with pesticide chemicals on raw agricultural commodities, merely reflects the fact that residues in that category are already covered by the Pesticide Chemicals Amendment of 1954. The law provides for the submission of petitions for the use of food additives and for us to issue regulations in this field where proper. I will not try to detail what needs to be in the petition other than to say that this calls for full information about the product, its toxicity, its chemistry and its proposed uses.

Under the extension provision of the law, we have published such extension authorizations for over 900 substances and classes of substances, some being direct additives, but a great many are in the category of packaging and equipment components. Drug items which are food additives are eligible for such extensions.

Those who have obtained such extensions have passed the first hurdle. They have convinced the FDA that the items involved can continue to be used through March 5, 1961, in the same way as they were used prior to January 1, 1958, without undue hazard to the public health. We cannot say too strongly, however, that getting over this first hurdle is not reaching the finish line. There is still much to be done, and perhaps the worst mistake in this field would be for industry people to feel that the extension lists have solved their problems. Remember, each extension expires on March 6, 1961, so petitions for food additive regulations should get to us in good season so they can be handled before that date.

I think it came as a surprise to some groups represented here today to learn that the food-additives amendment applies to subtances added to animal feed. This, however, goes back to the basic definition of "food" in the 1938 Act, which defines this term in part as articles used for food or drink for man or other animals and articles used for components of any such article. Thus, when a product meeting the definition of food additive is incorporated into animal feeds—whether this be for growth promotion, disease prevention, treatment of disease or other purposes—the provisions of the food-additives amendment

must be met. Actually, I doubt that this application of the law would have been the subject of a great deal of concern were it not for the so-called Delaney Clause in the food-additives amendment, which specifically prohibits the issuance of any food-additive regulation authorizing the use of an ingredient which has been shown to cause cancer on ingestion by man or animal or has been shown to cause cancer by other tests appropriate for the evaluation of food additives.

This clause has been debated pro and con most extensively. This Department is clearly on record as being in favor of it, although we do hope for an amendment that will authorize us to take steps which will get rid of the inequities we now have where those who have prior authorization by way of new-drug applications can continue to add a product like diethylstilbestrol to their feed, whereas their competitors cannot now get such authorization. Secretary Flemming has recommended to the Congress that the Delaney Clause be modified so that it will not be applicable in the case of animal feed where there is evidence to demonstrate that the additive does not cause cancer in the animal and is not present in the edible products of the animal at the time of slaughter. Until the law is changed, however, we have no choice but to enforce it as was announced in our policy statement of May, 1959.

Perhaps more surprising to some of the members of this group was a realization that some therapeutic agents are to be classed as food additives, or at least need to be investigated to determine whether or not they are food additives. If a drug is given to a food-producing animal, the edible portions are classed as adulterated if that drug or its metabolites which are not generally recognized as safe or are not subject to prior sanction remain in or on those edible portions such as milk or meat. This would be legalized by an appropriate food-additive regulation.

It must be remembered that, under the law, we cannot take action to authorize a product for one use, when that would then result in violation under another section of the statute. Thus, where we conclude that there is a food-additive problem involved, we are unable to make new-drug applications or Antibiotic Form 10's effective unless and until the food-additive feature is dealt with at the same time. We are told that this policy is serving to stifle research in the field of therapeutic agents for animals and in the field of medicated feeds. This is on the basis of the claim that the economics of such a situation

prevent manufacturers from going beyond the development of the product and field tests to determine whether it is effective for the purpose intended.

We, of course, recognize that right of any manufacturer to decide how much research he wants to engage in, but we do not recognize that the cost of finding out whether residues of such substances remain in our food supply—and, if so, whether they present a hazard to health —can be a factor in our evaluation.

We have questioned whether this requirement—or the Delaney Clause, for that matter—has resulted in a great decrease in research, although we recognize that as the Delaney Clause now stands, it would not appear wise to conduct research on a proposed feed additive which is known to produce cancer on ingestion.

A drug which might be used right up to the time of slaughter may call for a withdrawal period to insure no residue of that drug in the edible parts of the animal. In such a case, a food-additive regulation is called for. Another application would be the treatment of a producing cow with an antibiotic where we have a tolerance of zero for residues for the antibiotic in the milk. This would be met by a caution in the labeling which warns that the milk is not to be marketed as food for a specified period after treatment. I assume that many of you are familiar with our program and the surveys on milk for the presence of antibiotic and pesticide residues but if there are any questions along this line, I will be glad to try to answer them later. [These remarks were directed to the audience.] I should add, however, that particularly in the field of antibiotic residues we have been very pleased with the improvement shown during the past several months as demonstrated by the results of examination not only by governmental agencies but by industry laboratories as well.

In the pesticide chemical field, labels are required to be registered with the Department of Agriculture. Before such registration is granted, that department evaluates the directions for use to see that these directions, if followed, will result in the production of crops which do not carry illegal residues. In the field of medicated feeds and in some animal therapeutic agents, we have a comparable provision in that directions for use often call for withdrawal periods prior to slaughter—just as with milk which must be discarded after treatment of the cows with potent drugs. We can only urge that all who use these various additive preparations read and follow these restric-

tive directions so that there will be no case where the milk or meat is found to carry residues which make the product illegal. We think the veterinarians of this country can assist us in the necessary educational work along these lines, and we sincerely hope they will do so.

We believe it must be kept in mind that if we authorize the use of a feed additive, for example, which calls for a 48-hour withdrawal period prior to slaughter and then we find that there is widespread disregard of this direction, we must do more than merely deal with the illegal meat products which result from such a practice. We believe we must re-evaluate the original authorization, because there is no point in keeping a regulation which is not being met; the alternative is to change the regulation to eliminate the authorization to use the specific additive.

Particular mention should be made of experimental use on food-producing animals of various drugs or other items which are classed as food additives. We have issued a regulation under the food-additives amendment which authorizes the interstate shipment of new food additives for investigational use provided these are clearly labeled to show that they are for such experimental use by qualified experts and not for human food or food other than for laboratory animals. This means that, for example, if the experimental use is with cattle, at the conclusion of the experiment those cattle are not suitable to be sent to the slaughter house, since to do so would not be in conformity with the authorization for getting the new food additive in the first place. We realize that it may be possible to demonstrate that, after a specific period of time, none of the food additive remains in the edible portions of the animal. In such a case it could be suitable to remove that particular animal from the category of a "laboratory" animal at such time, but good scientific evidence showing no residue must be available before any such decision can be made.

We think this food-additives amendment is workable; we realize there have been many problems needing solution and that some of them have not as yet been completely solved. If there is, however, a recognition on the part of all concerned that this is a law not only for the protection of the consumer but one which will also in the long run benefit legitimate producers, and if we can all work together to solve the problems which arise, we will have sound authorizing regulations. Then, the objectives of this law will be well on their way to being met. **[The End]**

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